Organic LETTERS

Letter

pubs.acs.org/OrgLett

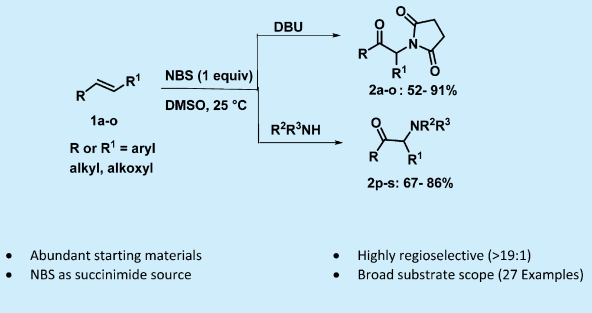
Regioselective Oxo-Amination of Alkenes and Enol Ethers with *N*-Bromosuccinimide−Dimethyl Sulfoxide Combination: A Facile Synthesis of α-Amino-Ketones and Esters

Pragati K. Prasad,[‡] Rambabu N. Reddi,[‡] and Arumugam Sudalai*[,†]

[†]Chemical Engineering and Process Development Division, National Chemical Laboratory, Pashan Road, Pune, 411008, India

Supporting Information

ABSTRACT: An unprecedented conversion of alkenes and enol ethers to the corresponding α-imido carbonyl compounds with excellent regioselectivity and yields has been developed. This oxo-amination process employs readily available *N*-bromosuccinimide (NBS) and secondary amines as N-sources and dimethyl sulfoxide (DMSO) as the oxidant and also leads to the production of amino alcohols in a single step on reduction, thus broadening the scope of this operationally simple reaction. For the first time, the formation of reactive Me_2S^+-O-Br species generated by the interaction of NBS with DMSO has been proven.



The vicinal heterodifunctionalization of alkenes (i.e., the addition of two distinct functional groups across the C=C bond) in a single operation (e.g., amino-, halo- or azido-hydroxylation) has become an important area due to its applicability to the pharmaceuticals, agrochemicals, and fine chemicals industries.[1] This process can proceed via metal or metal-free catalysis that reduces waste generation and laborious isolation and purification activity, often leading to products with broad structural diversity, thus contributing to both step and atom economy. While considerable progress has been made in oxo-functionalization (e.g., oxo-halogenation,[2] oxo-hydroxylation,[3] oxo-nitrogenation,[3b,c] and oxo-acyloxylation[4]) of alkenes under metal-free oxidative conditions, no report exists in the literature, to the best of our knowledge, on the regioselective oxo-amination of alkenes that directly affords α-amino carbonyl compounds.

α-Amino carbonyl compounds are useful structural scaffolds in both synthetic and medicinal chemistry because they exhibit a wide range of biological activities (e.g., antidepressant, appetite suppressant, antiplatelet properties, etc.).[5] Most of the strategies developed to date for the synthesis of α-aminoketones utilize either α-amination of carbonyl compounds using nitrogen electrophiles[6] or a nucleophilic displacement reaction of α-haloketones with amines.[7] However, their scope is rather limited by the scarcity of nitrogen electrophiles as well as the requirement of prefunctionalized haloketones. Recently, direct oxidative coupling of ketones with nucleophilic amines has been reported under both metal/metal-free conditions.[8] Nevertheless, addressing regioselectivity in the α-functionalization of ketone is of prime concern in these reported methods. Thus, a mild synthetic procedure that employs readily available starting materials and overcomes the above difficulties is desirable for regioselective synthesis of α-amino ketones.

Dimethyl sulfoxide (DMSO) has recently been used as the stabilizing agent for halogen/chalcogen cations and thus can serve as a powerful reagent for alkene difunctionalization.[9] On the other hand, *N*-bromosuccinimide (NBS) is mainly used as an electrophilic[10] or radical bromine source[11] and quite recently as a nucleophilic nitrogen source.[12] The combination of DMSO−NBS has become a powerful reagent system for selective oxidation of alkynes and alkenes to give 1,2-diketones[13] and epoxide/bromohydrins,[14] respectively. Recently, we have reported oxo-acyloxylation[4] of alkenes under basic conditions using the NBS−DMSO combination to give α-acyloxy ketones **4** with carboxylic acid as an O-nucleophile. In this letter, we wish to report that oxidative amination of alkenes and enol ethers proceeds regioselectively to afford α-amino carbonyl compounds **2a−s** in high yields employing NBS or a secondary amine as the N-source and DMSO as the oxidant (Scheme 1).

In order to study this reaction, styrene (1 mmol) was treated with NBS (1 mmol) and DBU (1 mmol) at 25 °C in DMSO for 8 h, which led to isolation of α-ketoimide **2a** in 86% yield with excellent regioselectivity (Table 1).[15] Gratifyingly, inorganic bases such as K_2CO_3 and KO^{t}Bu were also effective in giving **2a** in 64% and 58% yields, respectively (entries 3−4). The reaction, however, failed to give the required product **2a** when other organic solvents such as THF, CH_3CN, CH_2Cl_2, 1,4-dioxan, and DMF were employed. With other *N*-halosuccinimides (halo = I and Cl), **2a** was indeed obtained in 85% and 43% yields, respectively (entries 5−6). Furthermore, lowering the amount of DBU to 20 mol % resulted in a poor yield of **2a** (18%). The reaction temperature was also found to be critical in determining product selectivity. For instance, at 60 °C, bromohydrin **11** was isolated as the major product (47%), while at 10 °C epoxide **12**

Received: December 14, 2015

DOI: 10.1021/acs.orglett.5b03540
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Oxo-acyloxylation and Oxo-amination of Alkenes

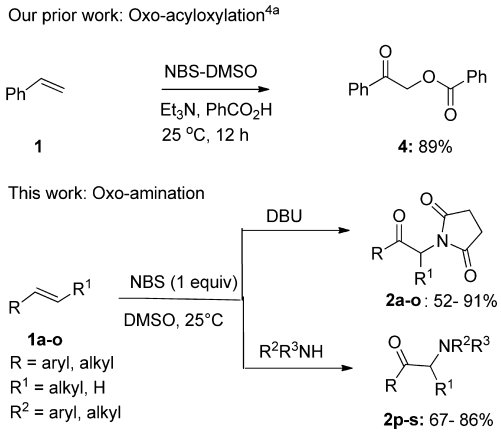
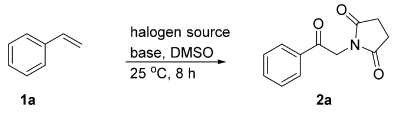


Table 1. Oxo-amination of Styrene: Optimization Studies[a]



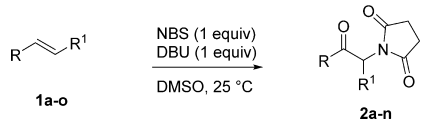
no.	halogen source (1 equiv)	base (1 equiv)	yield[b] of **2a** (%)
1	NBS	DBU	86 (18)[c] (25)[d] (12)[e]
2	NBS	Et_3N	59
3	NBS	KO^{t}Bu	64
4	NBS	K_2CO_3	58
5	NIS	DBU	85
6	NCS	DBU	43
7	NBS	DBU (20 mol %)	18

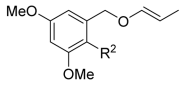
[a]Reaction conditions: styrene (1 mmol), base (1 mmol), halogen source (1 mmol) in anhyd. DMSO, 25 °C, 8 h. [b]Isolated yield after column chromatographic purification. [c]When DMSO was used as 5 equiv in the presence of CH_2Cl_2. [d]Reaction performed at 10 °C. [e]Reaction performed at 60 °C.

was obtained in a major amount along with **2a** (entry 1; values corresponding to footnotes d, e). A combination of NBS (1 equiv), and DBU (1 equiv) in dry DMSO at 25 °C was thus chosen as optimal for the oxo-amination process.

In order to determine its scope, a variety of other olefins were examined under the optimized reaction conditions and the results are summarized in Table 2. Styrenes bearing different substituents on the aromatic nucleus such as Cl, Me (neutral), OMe (electron-donating), fused phenyl, etc. were found to be excellent substrates for the oxo-amination process affording the corresponding α-ketoimides (**2a**−**d** and **2f**−**g**) in 84−91% yields and excellent regioselectivities (19:1) (Table 2, entries 1−4, 6−7). A strongly electron-withdrawing substrate such as 4-nitrostyrene afforded the desired product **2e** in moderate yield (52%) (entry 5). Also, internal alkenes such as β-methylstyrene and indene underwent this oxidative process smoothly giving **2h** and **2i** in 85% and 81% yields, respectively (entries 8−9). Notably, aliphatic alkenes (**1j**−**l**) gave the corresponding products in high yields (79−84%), thus establishing the generality of this protocol (entries 10−12). Remarkably, enol ethers **1m** and **1n** gave the corresponding imidoesters **2m** and **2n** in 82% and 71% yields, respectively which are essentially α-amino acid surrogates (entries 13−14). Activated substrate **1o** underwent oxo-amination as well as concomitant bromination to afford **2n** in 73% yield. Interestingly, α-methylstyrene (**1p**), under the optimized reaction conditions, gave the corresponding allylic imide **5** (ketone formation at tertiary position is intrinsically not possible hence the formed tertiary bromide undergoes elimination) in 68% yield (Scheme 2).

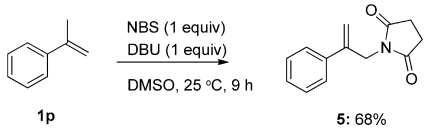
Table 2. Oxo-amination: Scope of Alkenes and Enol Ethers



entry	alkene, (R, R^1) (**1a-o**)	product (**2a-n**)	time (h)	yield (%)[b]
1	styrene (**1a**)	**2a**	8	86
2	4-Me styrene (**1b**)	**2b**	6.5	89
3	4-Cl styrene (**1c**)	**2c**	6	91
4	4-OMe styrene (**1d**)	**2d**	7	84
5	4-NO_2 styrene (**1e**)	**2e**	8	52
6	3-Me styrene (**1f**)	**2f**	6	90
7	2-vinylnaphthalene (**1g**)	**2g**	5.5	85
8	β-methylstyrene (**1h**)	**2h**	5	85
9	indene (**1i**)	**2i**	6.5	81
10	1-hexene (**1j**)	**2j**	7	82
11	1-octene (**1k**)	**2k**	7.5	84
12	cyclohexene (**1l**)	**2l**	7	79
13	ethyl vinyl ether (**1m**)	**2m**	4.5	82
14	 R^2 = Br; (**1n**) R^2 = H; (**1o**)	**2n**	5.5	71[c] 73[d]

[a]Reaction conditions: alkenes (1 mmol), DBU (1 mmol), NBS (1 mmol); in anhyd. DMSO, 25 °C, t (h). [b]Isolated yield after column chromatographic purification. [c]2 equiv of NBS was used. [d]Yield of **2n** corresponds to substrate **1o** in 7 h.

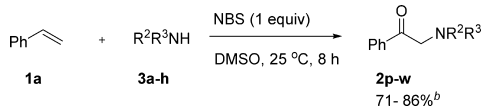
Scheme 2. Allylic Imidation of α-Methylstyrene



Next, it was of interest to study the scope of amine sources (Table 3). Thus, when styrene was treated with NBS and DBU (1 equiv each) in the presence of imidazole as a nucleophilic amine source, the corresponding amino ketone **2p** was obtained in 32% yield along with major amount of **2a** (48% yield). Further investigation however revealed that, in the absence of DBU, **2p** was obtained in 86% yield. Interestingly, benzimidazole and benzotriazole also gave **2q** and **2r** in 85% and 83% yields, respectively. Surprisingly, with *N*-methyl formamide, oxo-amination proceeds to give 2-(methylamino)-1-phenylethan-1-one (**2s**) in 79% yield. This may be explained in terms of basic hydrolysis of initially formed ketoamide during workup.[16] With aliphatic secondary amines such as pyrrolidine, morpholine, *N*-methylpiperazine, and diethylamine, the desired α-ketoamides **2t**−**v** were obtained in 72%, 74%, 68%, and 71% yields, respectively. However, in the case of primary amines, complex reaction mixtures were obtained.

DOI: 10.1021/acs.orglett.5b03540
Org. Lett. XXXX, XXX, XXX−XXX

Table 3. Oxo-Amination: Scope of Amines[a]

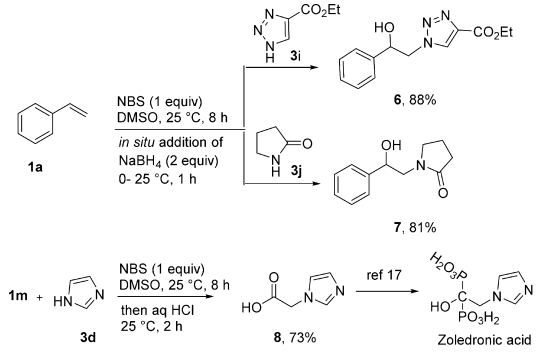


entry	amine source	product	yield of **2** (%)[b]
1	imidazole (**3a**)	**2p**	86
2	benzimidazole (**3b**)	**2q**	85
3	benzotriazole (**3c**)	**2r**	83
4	N-Me formamide (**3d**)	**2s**	79[c]
5	piperidine (**3e**)	**2t**	72
6	morpholine (**3f**)	**2u**	74
7	*N*-Me piperazine (**3g**)	**2v**	71
8	diethylamine (**3j**)	**2w**	68

[a]Reaction conditions: alkene (1 mmol), amine source (1 mmol), anhyd. DMSO, 25 °C, 10 h. [b]Isolated yield after column chromatographic purification. [c]*In situ* decarbonylation took place to afford 2-(methylamino)-1-phenylethan-1-one.

In order to extend its scope further, some "one-pot" reactions were carried out (Scheme 3). When **1a** was treated with triazole

Scheme 3. Other One-Pot Reactions for the Synthesis of Useful Intermediates from Alkenes

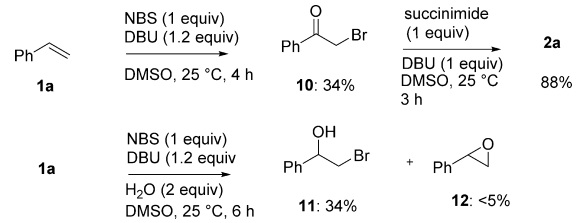


carboxylate in NBS–DMSO conditions, followed by $NaBH_4$ reduction, the triazole derivative **6** was obtained in 88% yield. In another experiment, the selective "one-pot" reduction has also been successfully demonstrated by treatment of **1a** with 2-pyrrolidone and its subsequent *in situ* reduction with $NaBH_4$ afforded β-hydroxyamide **7** in 81% yield.

This methodology is amply demonstrated in the formal synthesis of zoledronic acid **9**, used in the treatment of osteoporosis. Intermediate **8** was prepared by oxo-amination of ethyl vinyl ether (**1m**) with imidazole (**3d**) followed by acid hydrolysis in a single step. Furthermore, the enantioselective version of this oxoamination process with β-methylstyrene as substrate using (−)-spartein as a chiral base, however, resulted in a poor yield (12%) of **2h** with no asymmetric induction.

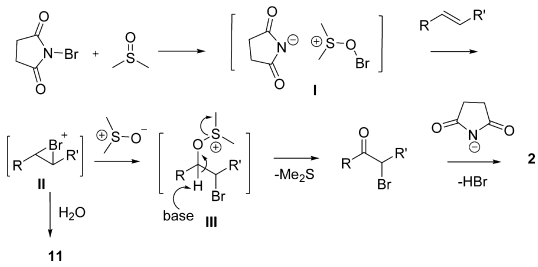
To understand its mechanistic course, the following experiments were conducted. (i) When styrene was treated with NBS–DBU in DMSO for a shorter reaction time (4 h), phenacyl bromide **10** was isolated in 34% yield. (ii) Further, when phenacyl bromide was treated with succinimide in the presence of DBU in DMSO, the corresponding α-ketoimide **2a** was obtained, confirming that phenacyl bromide is undoubtedly the key intermediate in the reaction. (iii) When equimolar amounts of NBS and DMSO were mixed at room temperature, (bromooxy)dimethylsulfonium ion (**I**) was identified by mass spectral analysis (m/z 156.9334 [M^+] and 158.9357 [M^++2]) and its counter succinimide anion by ^{13}C NMR analysis (δ 177.8 due to carbonyl carbon) suggestive of nucleophilic succinimide anion formation in DMSO solvent (corroborated by Scheme 2 as well). (iv) The interaction of NBS and DBU can be eliminated in the present reaction conditions, since the reaction proceeds with other bases as well (Table 1). (v) When 2 equiv of water were added in the reaction mixture, the corresponding bromohydrin **11** was obtained, suggesting the formation of bromosulfonium intermediate **III** (Scheme 5).

Scheme 5. Control Experiments to Probe into the Mechanism



Based on our experimental results and literature precedence,[16] a probable mechanism for the oxo-amination of alkenes is outlined in Scheme 6. Initially, NBS reacts with DMSO to form

Scheme 6. Probable Mechanism for Oxo-amination of Alkenes

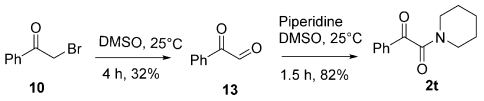


the bromosulfoxonium cation (**I**) and succinimide counteranion. Styrene then reacts with bromosulfoxonium species to form intermediate **III** (via bromonium ion intermediate **II**), which readily undergoes Me_2S elimination to provide an α-bromo carbonyl compound. This is followed by displacement of the bromide ion with a succinimide anion to form the corresponding α-ketoimides. On the other hand, under aqueous conditions, intermediate **III** is preferentially attacked by water to give bromohydrin **12** and subsequently epoxide **13** is formed under basic conditions.

In order to account for the formation of α-ketoamides **2t–w** the following control experiments were performed (Scheme 7). (i) Since phenacyl bromide (**10**) was isolated as the key

DOI: 10.1021/acs.orglett.5b03540
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 7. Course of the Reaction in Ketoamide Formation



intermediate in the reaction, it was then treated with piperidine in anhydrous DMSO, which gave diketoamide **2t** in 84% yield.[18a] (ii) Furthermore, in the absence of piperidine in the reaction medium, phenacyl bromide in DMSO gave the corresponding phenylglyoxal (**13**) in 32% yield.[18b,c] The formed phenylglyoxal, when treated with piperidine in DMSO, afforded the α-ketoamide **2t** in 82% yield. It is thus believed that the reaction proceeds through intermediate phenacyl bromide and phenylglyoxal.

To summarize, we have developed, for the first time, highly regioselective oxo-aminations of alkenes and enol ethers to afford α-amino carbonyl compounds in high yields; also, a "one-pot" process for the synthesis of vicinal amino alcohol derivatives has also been demonstrated. Additionally, oxidative coupling of alkenes and secondary amines for the synthesis of α-ketoamides has been reported. More importantly, the (bromooxy)-dimethylsulfonium ion (**I**) as a reactive species, generated from an inexpensive NBS−DMSO−DBU oxidative system, has been identified for this oxo-amination reaction. We believe that this operationally simple and mild protocol would serve as a prominent method and find tremendous applications in the synthesis of widely occurring natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03540.

Experimental procedures, product characterization, and copies of NMR spectra for **2a−w**, **4−13** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: a.sudalai@ncl.res.in.

Author Contributions

‡P.K.P. and R.N.R. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

P.K.P. and R.N.R. thank CSIR, New Delhi for the award of research fellowships and thank CSIR, New Delhi and DST-SERB (No. SB/S1/OC-42/2014) for financial support. The authors are also thankful to Dr. V. V. Ranade, Chair, Chem. Engg. & Process Develop. for his constant encouragement.

■ REFERENCES

(1) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (b) Chemler, S. R.; Bovino, M. T. *ACS Catal.* **2013**, *3*, 1076.

(2) (a) Moorthy, J. N.; Senapati, K.; Singhal, N. *Tetrahedron Lett.* **2009**, *50*, 2493. (b) Patil, R. D.; Joshi, G.; Adimurthy, S.; Ranu, B. C. *Tetrahedron Lett.* **2009**, *50*, 2529. (c) Nobuta, T.; Hirashima, S.; Tada, N.; Miura, T.; Itoh, A. *Synlett* **2010**, *2010*, 2335.

(3) Murahashi, S.; Saito, T.; Hanaoka, H.; Murakami, Y.; Naota, T.; Kumobayashi, H.; Akutagawa, S. *J. Org. Chem.* **1993**, *58*, 2929. (b) Venkatramreddy, M.; Kumareswaran, R.; Vankar, Y. D. *Tetrahedron Lett.* **1995**, *36*, 6751. (c) Villar, A.; Hoevelmann, C. H.; Nieger, M.; Muniz, K. *Chem. Commun.* **2005**, *26*, 3304. (d) Muniz, K.; Hovelmann, C. H.; Villar, A. A.; Vicente, R.; Streuff, J.; Nieger, M. *J. Mol. Catal. A: Chem.* **2006**, *251*, 277.

(4) (a) Reddi, R. N.; Prasad, P. K.; Sudalai, A. *Org. Lett.* **2014**, *16*, 5674. (b) Reddi, R. N.; Malekar, P. V.; Sudalai, A. *Org. Biomol. Chem.* **2013**, *11*, 6477.

(5) (a) Meltzer, P. C.; Butler, D.; Deschamps, J. R.; Madras, B. K. *J. Med. Chem.* **2006**, *49*, 1420. (b) Carroll, F. I.; Blough, B. E.; Abraham, P.; Mills, A. C.; Holleman, J. A.; Wolckenhauer, S. A.; Decker, A. M.; Landavazo, A. K.; McElroy, T.; Navarro, H. A.; Gatch, M. B.; Forster, M. J. *J. Med. Chem.* **2009**, *52*, 6768. (c) Bouteiller, C.; Becerril-Ortega, J.; Marchand, P.; Nicole, O.; Barre, L.; Buisson, A.; Perrio, C. *Org. Biomol. Chem.* **2010**, *8*, 1111. (d) Myers, M. C.; Wang, J.-L.; Iera, J. A.; Bang, J.-K.; Hara, T.; Saito, S.; Zambetti, G. P.; Appella, D. H. *J. Am. Chem. Soc.* **2005**, *127*, 6152.

(6) (a) McDonald, S. L.; Wang, Q. *Chem. Commun.* **2014**, *50*, 2535. (b) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11827. (c) Miura, T.; Morimoto, M.; Murakami, M. *Org. Lett.* **2012**, *14*, 5214. (d) Takeda, T.; Terada, M. *J. Am. Chem. Soc.* **2013**, *135*, 15306. (e) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (f) Maji, B.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 8714. (g) Kano, T.; Shirozu, F.; Maruoka, K. *Org. Lett.* **2014**, *16*, 1530. (h) Xu, C.; Zhang, L.; Luo, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 4149. (i) Cecere, G.; König, C. M.; Alleva, J. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11521. (j) Wang, S.-G.; Yin, Q.; Zhuo, C.-X.; You, S.-L. *Angew. Chem., Int. Ed.* **2015**, *54*, 647. (k) Nan, J.; Liu, J.; Zheng, H.; Zuo, Z.; Hou, L.; Hu, H.; Wang, Y.; Luan, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 2356. (l) Yang, X.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3205.

(7) (a) Hill, J.; Zakaria, M.; Mumford, D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2455. (b) Yadav, J. S.; Subba Reddy, B. V.; Srinivas, M. *Chem. Lett.* **2004**, *33*, 882.

(8) (a) Evans, R. E.; Zbieg, J. R.; Zhu, S.; Li, W.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 16074. (b) Jiang, Q.; Xu, B.; Zhao, A.; Jia, J.; Liu, T.; Guo, C. *J. Org. Chem.* **2014**, *79*, 8750. (c) Lamani, M.; Prabhu, K. R. *Chem. - Eur. J.* **2012**, *18*, 14638. (d) Jing, Y.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2014**, *16*, 4932. (e) Zhang, X.; Wang, L. *Green Chem.* **2012**, *14*, 2141.

(9) Ashikari, Y.; Shimizu, A.; Nokami, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2013**, *135*, 16070.

(10) (a) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Lett.* **2003**, *32*, 932. (b) Andersh, B.; Murphy, D. L.; Olson, R. J. *Synth. Commun.* **2000**, *30*, 2091.

(11) (a) Djerassi, C. *Chem. Rev.* **1948**, *43*, 271. (b) Horner, L.; Winkelmann, E. H. *Angew. Chem.* **1959**, *71*, 349. (c) Futamura, S.; Zong, Z.-M. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 345. (d) Greenwood, F. L.; Kellert, M. D.; Sedlak, J. 4-Bromo-2-heptene. *J. Org. Synth., Coll.* **1963**, *4*, 108.

(12) (a) Wei, Y.; Lin, S.; Liang, F. *Org. Lett.* **2012**, *14*, 4202. (b) Wei, Y.; Lin, S.; Liang, F.; Zhang, J. *Org. Lett.* **2013**, *15*, 852. (c) Wei, Y.; Liang, F.; Zhang, X. *Org. Lett.* **2013**, *15*, 5186.

(13) Wolfe, S.; Pilgrim, W. R.; Garrard, T. F.; Chamberlain, P. *Can. J. Chem.* **1971**, *49*, 1099.

(14) Majetich, G.; Shimkus, J.; Li, Y. *Tetrahedron Lett.* **2010**, *51*, 6830.

(15) Reddi, R. N.; Prasad, P. K.; Sudalai, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 14150.

(16) O'Brien, J. F. *J. Phys. Chem.* **1995**, *99*, 12759.

(17) Floyd, M. B.; Du, M. T.; Fabio, P. F.; Jacob, L. A.; Johnson, B. D. *J. Org. Chem.* **1985**, *50*, 5022.

(18) (a) Deshidi, R.; Devari, S.; Shah, B. A. *Eur. J. Org. Chem.* **2015**, *2015*, 1428. (b) Dutta, S.; Kotha, S. S.; Sekar, G. *RSC Adv.* **2015**, *5*, 47265. (c) Andresen, B. D.; Biemann, K. *J. Labelled Compd. Radiopharm.* **1978**, *15*, 479.

DOI: 10.1021/acs.orglett.5b03540
Org. Lett. XXXX, XXX, XXX−XXX