Organic LETTERS

Letter

pubs.acs.org/OrgLett

Metal-Free Oxidative 1,2-Arylmethylation Cascades of *N*-(Arylsulfonyl)acrylamides Using Peroxides as the Methyl Resource

Fang-Lin Tan,[†] Ren-Jie Song,*[,‡] Ming Hu,[†] and Jin-Heng Li*[,†,‡]

[†]State Key Laboratory of Chemo/Biosensing and Chemometrics, Hunan University, Changsha 410082, China

[‡]Key Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle, Nanchang Hangkong University, Nanchang 330063, China

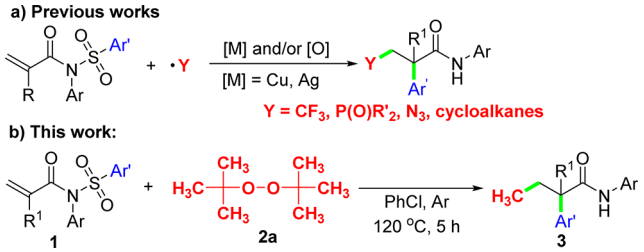
Supporting Information

ABSTRACT: A new, metal-free oxidative 1,2-arylmethylation cascades of *N*-(arylsulfonyl)acrylamides for the assembly of 2,2-disubstituted-*N*-arylbutanamides containing an all-carbon quaternary center is presented. This reaction enables the one-step formation of two new C−C bonds through a sequence of methylation/1,4-aryl migration/desulfonylation using an organic peroxide as the methyl resource with a broad substrate scope and excellent functional group tolerance.

Difunctionalization of alkenes is one of the most important methods for increasing molecular complexity in synthesis, which can simultaneously construct two new chemical bonds in one-step.[1,2] As a result, considerable efforts have been devoted to develop new efficient strategies for the alkene difunctionalization.[3] Among them, oxidative dicarbo-functionalization are particularly appealing, which enable the formation of two new C−C bonds in a single reaction.[4] However, approaches for the oxidative 1,2-arylalkylation of alkenes are less abundant, and the majority are restricted to transformations of *N*-arylacrylamides to oxindoles and related heterocycles via a sequence of intramolecular C(sp^2)−H functionalization and cyclization.[5] Recently, attention has been attracted on the difunctionalization of *N*-(arylsulfonyl)acrylamides, which proceeded involving aryl migration and desulfonylation.[6] In 2013, Nevado and co-workers first reported a copper-catalyzed 1,2-aryltrifluoromethylation of the alkene moieties in *N*-(arylsulfonyl)acrylamides via a radical-mediated trifluoromethylation, aryl migration/desulfonylation tandem process[6b] leading to *α*-aryl-*β*-trifluoromethyl amides.[7] Subsequently, some new radical-mediated strategies, including 1,2-arylphosphonylation,[6a] 1,2-arylazidation,[6g] and 1,2-arylalkylation,[6e] for the transformations of *N*-(arylsulfonyl)acrylamides have been developed (Scheme 1a). Although the oxidative 1,2-arylalkylation of *N*-(arylsulfonyl)acrylamides has been described by the group of Zhu, it was limited to the use of cycloalkanes as the alkyl resources. Further, to our knowledge, methods for the 1,2-arylmethylation cascades of *N*-(arylsulfonyl)acrylamides have never been reported, despite the obvious synthetic utility of the methylation reaction in chemistry, especially in medicinal chemistry.[8−10]

Herein, we report a new metal-free oxidative 1,2-arylmethylation cascade of *N*-(arylsulfonyl)acrylamides with peroxides for the synthesis of 2,2-disubstituted-*N*-arylbutanamides containing an all-carbon quaternary center. This radical-mediated reaction employs peroxides as the methyl resource, thus enabling the one-step formation of two C−C bonds through a sequence of methylation, aryl migration, and desulfonylation (Scheme 1b).

Scheme 1. Difunctionalization Cascades of *N*-(Arylsulfonyl)acrylamides

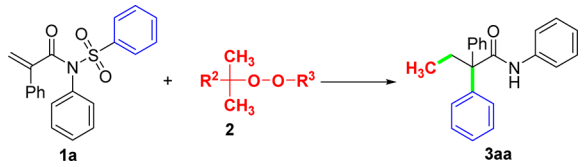


We began our studies by examining the 1,2-arylmethylation cascades of *N*,2-diphenyl-*N*-(phenylsulfonyl)acrylamide (**1a**) with peroxides (Table 1). Pleasingly, treatment of acrylamide **1a** with di-*tert*-butyl peroxide (DTBP; **2a**) in PhCl under argon atmosphere at 120 °C for 5 h afforded the desired product **3aa** in 72% yield (entry 1). Encouraged by the results, a series of other peroxides, including dicumylperoxide **2b** (DCP), *tert*-butyl peroxybenzoate **2c** (TBPB), *tert*-butyl hydroperoxide **2d** (TBHP; in decane), and aqueous TBHP **2e**, was examined (entries 2−5): each of which could serve as the methyl resource for the reaction but was less reactive than DTBP in terms of yields. Notably, the use of DCP **2b** exclusively resulted in the

Received: May 16, 2016

DOI: 10.1021/acs.orglett.6b01419
Org. Lett. XXXX, XXX, XXX−XXX

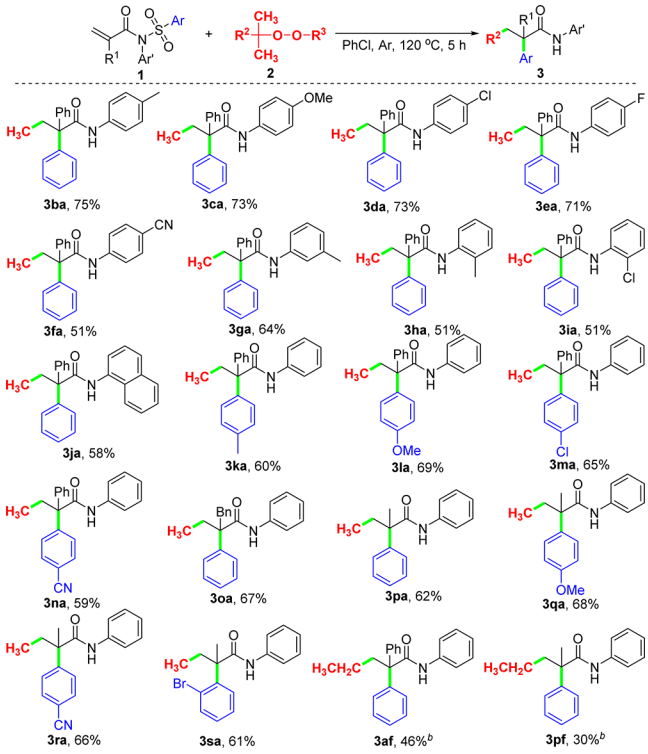
Table 1. Screening of Optimal Conditions[a]



entry	peroxide (equiv)	solvent	t (°C)	yield (%)[b]
1	DTBP **2a** (3)	PhCl	120	72
2	DCP **2b** (3)	PhCl	120	67
3	TBPB **2c** (3)	PhCl	120	38
4[c]	TBHP **2d** (3)	PhCl	120	15
5[d]	TBHP **2e** (3)	PhCl	120	14
6	DTBP **2a** (4)	PhCl	120	70
7	DTBP **2a** (2)	PhCl	120	52
8[e]	DTBP **2a** (3)	MeCN	120	38
9[f]	DTBP **2a** (3)	toluene	120	29
10	DTBP **2a** (3)	DMF	120	21
11	DTBP **2a** (3)	$PhCF_3$	120	64
12	DTBP **2a** (3)	*t*-BuOH	120	trace
13	DTBP **2a** (3)	PhCl	130	68
14	DTBP **2a** (3)	PhCl	110	24
15[g]	DTBP **2a** (3)	PhCl	120	65

[a]Reaction conditions: **1a** (0.2 mmol), **2**, solvent (2 mL), argon, and 5 h. [b]Isolated yield. [c]TBHP (anhydrous, 5 M in decane). [d]TBHP (70% in water). [e]A trace amount of cyano-containing product was detected by GC−MS analysis. [f]A trace amount of 1,2-benylmethylation product was detected by GC−MS analysis. [g]**1a** (726 mg, 2 mmol) for 8 h.

Scheme 2. Variation of the Acryl Sulfonamides (1)[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (3 equiv), PhCl (2 mL), argon, 120 °C, and 5 h. [b]2-Hydroperoxy-2-methylbutane (**2f**) (0.4 mmol) was used as ethyl source.

formation of the 1,2-phenylmethylation product **3aa**, not the 1,2-phenylphenylation product (entry 2). A screen of the amount of DTBP **2a** revealed 3 equiv of DTBP as the best choice (entries 6 and 7). Among the effect of solvent examined, the use of PhCl solvent turned out to be the most effective than the other solvents, such as MeCN, toluene, DMF, $PhCF_3$, and *t*-BuOH (entries 8−12). Further screening on the reaction temperature proved that the reaction at 120 °C gave the best yield (entries 1, 13, and 14). Gratifyingly, the scale of acrylamide **1a** up to 2 mmol was also viable for the synthesis of **3aa** in moderate yield (entry 15).

With the optimized reactions in hand, we set out to explore the scope of this oxidative 1,2-arylmethylation cascades protocol with respect to the *N*-(arylsulfonyl)acrylamides **1**, and the results are summarized in Scheme 2. The optimal conditions were compatible with a variety of *N*-aryl-*N*-(arylsulfonyl)acrylamides **1**, providing the corresponding products **3ba−sa** in moderate yields. Importantly, several substituents, namely, Me, OMe, Cl, F, and CN, on the aromatic ring of the *N*-aryl moiety were well-tolerated, and the reactive order of the substituents was *para* > *meta* > *ortho* in terms of yields (products **3ba−ia**). While *para*-Me-substituted substrate **1b** gave **3ba** in 75% yield, *meta*-Me-substituted substrate **1g** or *ortho*-Me-substituted substrate **1h** delivered the corresponding products **3ga** and **3ha**, respectively, in lower yields. Notably, *N*-(naphthalen-1-yl)-substituted substrate **1j** was also proved to be viable for furnishing **3ja**. Subsequently, the substitution effect on the aromatic ring of the *N*-(arylsulfonyl) moiety was investigated. Substrates **1k−n**, bearing a Me, a OMe, a Cl, or a CN group on the aryl ring of the *N*-(arylsulfonyl) moiety, were efficiently converted to the corresponding products **3ka−na** in moderate to good yields. Using substrates **1o** or **1p** with benzyl or methyl group at the 2 position of the acrylamides moiety smoothly assembled products **3oa** and **3pa**, respectively. In the case of *N*-phenyl-*N*-(arylsulfonyl)-methacrylamides **1q−s**, the reaction were successfully performed, giving **3qa−sa** in moderate yield. Notably, Cl, F, and Br groups could also survive, thereby facilitating additional modifications at the halogenated position (products **3da−ea**, **3ia**, **3ma**, and **3sa**).

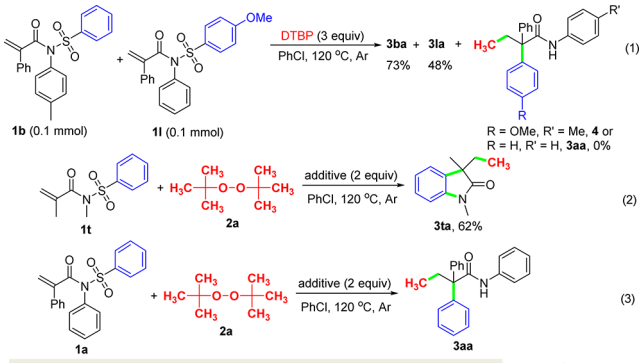
Gratifyingly, the optimal conditions were applicable to 1,2-arylethylation cascades of *N*-(arylsulfonyl)acrylamides (products **3af** and **3pf**). For example, substrate **1a** treated with 2-hydroperoxy-2-methylbutane (**2f**) exclusively afforded the 1,2-phenylethylation product **3af** in 46% yield.

To understand the mechanism, some control experiments were designed (Scheme 3). A mixture of two different acryl sulfonamides **1b** and **1l** was reacted with DTBP (**2a**) under the optimal conditions; no cross aryl-migrating products were obtained (eq 1). The results demonstrate that 1,4-aryl migration proceeds via an intramolecular process. To our surprise, *N*-alkyl substrate **1t** afford a cyclization product 3-ethyl-1,3-dimethylindolin-2-one (**3ta**), in 62% yield (eq 2). Notably, the reaction of *N*,2-diphenyl-*N*-(phenylsulfonyl)acrylamide (**1a**) with DTBP **2a** was completely inhibited when using a stoichiometric amount of radical scavengers, including TEMPO, 2,6-di-*tert*-butyl-4-methylphenol (BHT), and hydroquinone. Moreover, 1-methoxy-2,2,6,6-tetramethylpiperidine **5** was in situ detected by GC−MS analysis. These results suggest that the reaction may involve a radical process (eq 3).

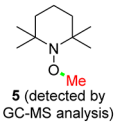
The plausible mechanism of this metal-free oxidative 1,2-arylmethylationcascades was proposed (Scheme 4).[3,6−10] DTBP readily generates methyl radical and acetone under heating. Addition of the methyl radical across the C−C double bond in *N*-(arylsulfonyl)acrylamides **1** affords the radical intermediate **A**,

DOI: 10.1021/acs.orglett.6b01419
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Control Experiments

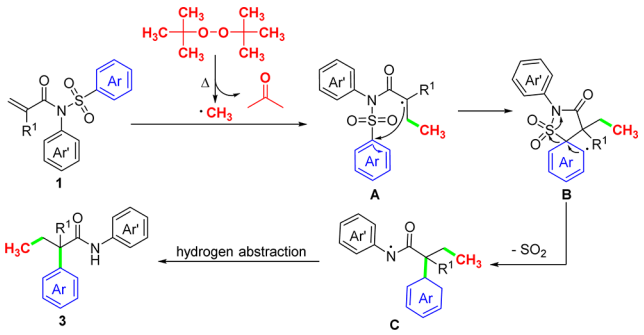


additive	yield of **3aa**
TEMPO	trace[a]
BHT	trace
hydroquinone	trace



[a]1-Methoxy-2,2,6,6-tetramethylpiperidine (**5**) was in situ detected by GC−MS analysis.

Scheme 4. Possible Mechanism



followed by intramolecular 5-*ispo*-cyclization, which forms the intermediate **B**. The intermediate **B** then transforms into the amidyl radical intermediate **C** via desulfonylation. Finally, hydrogen abstraction of the intermediate **C** gives the desired product **3**.

In summary, we have developed new, metal-free oxidative 1,2-arylmethylation cascades of *N*-(arylsulfonyl)acrylamides using organic peroxides as the methyl source through a sequence of methylation/aryl migration/desulfonylation. This reaction provides a simple and facile route to the straightforward synthesis of 2,2-disubstituted-*N*-arylbutanamides with a quaternary stereocenter with excellent functional group tolerance.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01419.

Descriptions of experimental procedures for compounds and analytical characterization (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: srj0731@hnu.edu.cn.
*E-mail: jhli@hnu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Natural Science Foundation of China (Nos. 21402046 and 21472039) for financial support.

■ REFERENCES

(1) (a) Patai, S., Ed. *The Chemistry of Alkenes*; Wiley Interscience: New York, 1964. (b) Oestrich, M., Ed. *The Mizoroki-Heck Reaction*; Wiley: Chichester, 2009. (c) de Meijere, A.; Meyer, F. E., Jr. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (d) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (e) Shimizu, Y.; Kanai, M. *Tetrahedron Lett.* **2014**, *55*, 3727. (f) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (g) Liu, G.; Wu, Y. *Top. Curr. Chem.* **2009**, *292*, 195. (h) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (i) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2012**, *45*, 1736.

(2) For selected reviews: (a) Li, G.; Chang, T.-T.; Sharpless, B. K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910. (d) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, *36*, 1153. (e) Wolfe, J. P. *Synlett* **2008**, *2008*, 2913. (f) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351. (g) Wolfe, J. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10224. (h) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083. (i) Merino, E.; Nevado, C. *Chem. Soc. Rev.* **2014**, *43*, 6598. (j) Romero, R. M.; Woste, T. H.; Muniz, K. *Chem. - Asian J.* **2014**, *9*, 972. (k) Chen, J.-R.; Yu, X.-Y.; Xiao, W.-J. *Synthesis* **2015**, *47*, 604. (l) Tang, S.; Liu, K.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2015**, *44*, 1070.

(3) For reviews on difunctionalization of alkenes, see: (a) Coombs, J. R.; Morken, J. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 2636. (b) Egami, H.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8294. (c) Hesp, K. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 2034. (d) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142. (e) Li, Y.-F.; Hari, D.-P.; Vita, M. V.; Waser, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 4436. (f) Reichard, H. A.; Micalizio, G. C. *Chem. Sci.* **2011**, *2*, 573. (g) Romero, R. M.; Woste, T. H.; Muniz, K. *Chem. - Asian J.* **2014**, *9*, 972. (h) Shimizu, Y.; Kanai, M. *Tetrahedron Lett.* **2014**, *55*, 3727. (i) Wu, K.; Liang, Y.; Jiao, N. *Molecules* **2016**, *21*, 352.

(4) (a) Wang, H.; Lu, Q.; Qian, C.; Liu, C.; Liu, W.; Chen, K.; Lei, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 1094. (b) Bergonzini, G.; Cassani, C.; Lorimer-Olsson, H.; Hoerberg, J.; Wallentin, C.-J. *Chem. - Eur. J.* **2016**, *22*, 3292. (c) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 8069. (d) Zheng, L.; Huang, H.; Yang, C.; Xia, W. *Org. Lett.* **2015**, *17*, 1034. (e) Sun, X.; Li, X.; Song, S.; Zhu, Y.; Liang, Y.-F.; Jiao, N. *J. Am. Chem. Soc.* **2015**, *137*, 6059. (f) Fan, J.-H.; Yang, J.; Song, R.-J.; Li, J.-H. *Org. Lett.* **2015**, *17*, 836. (g) Zheng, L.-W.; Huang, H.-L.; Yang, C.; Xia, W.-J. *Org. Lett.* **2015**, *17*, 1034.

(5) (a) Wang, S.-C.; Huang, X.-H.; Li, B.-W.; Ge, Z.-M.; Wang, X.; Li, R.-T. *Tetrahedron* **2015**, *71*, 1869. (b) Wang, G.; Wang, S.; Wang, J.; Chen, S.-Y.; Yu, X.-Q. *Tetrahedron* **2014**, *70*, 3466. (c) Zheng, L.-W.; Huang, H.-L.; Yang, C.; Xia, W.-J. *Org. Lett.* **2015**, *17*, 1034. (d) Wei, W.-T.; Zhou, M.-B.; Fan, J.-H.; Liu, W.; Song, R.-J.; Liu, Y.; Xie, P.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 3638.

(6) (a) Fuentes, N.; Kong, W.-Q.; Fernández-Sánchez, L.; Merino, E.; Nevado, C. *J. Am. Chem. Soc.* **2015**, *137*, 964. (b) Kong, W.-Q.; Casimiro, M.; Merino, E. A.; Nevado, C. *J. Am. Chem. Soc.* **2013**, *135*, 14480. (c) Kong, W.-Q.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 5078. (d) Fan, J.-H.; Yang, J.; Song, R.-J.; Li, J.-H. *Org. Lett.* **2015**, *17*, 836. (e) Zhang, H.-L.; Pan, C.-D.; Jin, N.; Gu, Z.-X.; Hua, H.-W.; Zhu, C.-J. *Chem. Commun.* **2015**, *51*, 1320. (f) Kong, W.-Q.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 13086. (g) Kong, W.-Q.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 2487.

(7) (a) Kong, W.-Q.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 13086. (b) Chen, Z.-M.; Bai, W.; Wang, S.-H.; Yang, B.-M.; Tu, Y.-Q.; Zhang, F.-M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9781. (c) Toda, Y.; Pink, M.; Johnston, J. N. *J. Am. Chem. Soc.* **2014**, *136*, 14734. (d) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 8069. (e) Bergonzini, G.; Cassani, C.; Lorimer-Olsson, H.; Horberg, J.; Wallentin, C. J. *Chem. - Eur. J.* **2016**, *22*, 3292. (f) Gao, Y.-Z.;

DOI: 10.1021/acs.orglett.6b01419
Org. Lett. XXXX, XXX, XXX−XXX

Li, X.-Q.; Chen, W.-Z.; Tang, G.; Zhao, Y.-F. *J. Org. Chem.* **2015**, *80*, 11398.

(8) For reviews, see: (a) Schonherr, H.; Cernak, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 12256. (b) Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215. (c) Challenger, F. *Chem. Rev.* **1945**, *36*, 315. (d) Matthews, R. G.; Smith, A. E.; Zhou, Z. S.; Taurog, R. E.; Bandarian, V.; Evans, J. C.; Ludwig, M. *Helv. Chim. Acta* **2003**, *86*, 3939. (e) Grewal, S. I.; Rice, J. C. *Curr. Opin. Cell Biol.* **2004**, *16*, 230. (f) Nakayama, J.-I.; Rice, J. C.; Strahl, B. D.; Allis, C. D.; Grewal, S. I. *Science* **2001**, *292*, 110. (g) Ei-ichi, N.; Hajime, M. *Org. Synth.* **1984**, *62*, 31. (h) Wienken, C. J.; Baaske, P.; Braun, D. *Nucleic Acids Res.* **2011**, *39*, 152.

(9) For recent examples, see: (a) Shamovsky, I.; deGraaf, C.; Alderin, L.; Bengtsson, M.; Bladh, H. k.; Börjesson, L.; Connolly, S.; Dyke, H. J.; van den Heuvel, M.; Johansson, H.; Josefsson, B.-G. r.; Kristoffersson, A.; Linnanen, T.; Lisius, A.; Männikkö, R.; Nordén, B.; Price, S.; Ripa, L.; Rognan, D.; Rosendahl, A.; Skrinjar, M.; Urbahns, K. *J. Med. Chem.* **2009**, *52*, 7706. (b) Gui, J.-H.; Zhou, Q.-H.; Pan, C.-M.; Yabe, Y.; Burns, A.; Collins, M.; Ornelas, M.; Ishihara, Y.; Baran, P. *J. Am. Chem. Soc.* **2014**, *136*, 4853. (c) Leung, C. S.; Leung, S. S. F.; Tirado-Rives, J.; Jorgensen, W. L. *J. Med. Chem.* **2012**, *55*, 4489. (d) Pan, F.; Lei, Z.-Q.; Wang, H.; Li, H.; Sun, J.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2063. (e) Araki, M.; Maeda, M.; Kawazoe, Y. *Tetrahedron* **1976**, *32*, 337. (f) Levy, M.; Szwarc, M. *Tetrahedron.* **1954**, *77*, 1949.

(10) For methylation using peroxides as the methyl resource, see: (a) Dai, Q.; Yu, J.-T.; Feng, X.-M.; Jiang, Y.; Yang, H.-T.; Cheng, J. *Adv. Synth. Catal.* **2014**, *356*, 3341. (b) Kubo, T.; Chatani, N. *Org. Lett.* **2016**, *18*, 1698. (c) Xia, Q.-Q.; Liu, X.-L.; Zhang, Y.-J.; Chen, C.; Chen, W.-Z. *Org. Lett.* **2013**, *15*, 3326. (d) Xu, Z.-B.; Yan, C.-X.; Liu, Z.-Q. *Org. Lett.* **2014**, *16*, 5670. (e) Zhang, Y.-H.; Feng, J.-Q.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, *130*, 2900. (f) Fan, J.-H.; Zhou, M.-B.; Liu, Y.; Wei, W.-T.; Ouyang, X.-H.; Song, R.-J.; Li, J.-H. *Synlett* **2014**, *25*, 657. (g) Zhu, Y.; Yan, H.; Lu, L.-H.; Liu, D.-F.; Rong, G.-W.; Mao, J.-C. *J. Org. Chem.* **2013**, *78*, 9898. (h) Dai, Q.; Yu, J.-T.; Jiang, Y.; Guo, S.-J.; Yang, H.-T.; Cheng, J. *Chem. Commun.* **2014**, *50*, 3865. (i) Guo, S.-J.; Wang, Q.; Jiang, Y.; Yu, J.-T. *J. Org. Chem.* **2014**, *79*, 11285. (j) Teng, F.; Cheng, J.; Yu, J.-T. *Org. Biomol. Chem.* **2015**, *13*, 9934.

DOI: 10.1021/acs.orglett.6b01419
Org. Lett. XXXX, XXX, XXX−XXX