Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX-XXX

pubs.acs.org/OrgLett

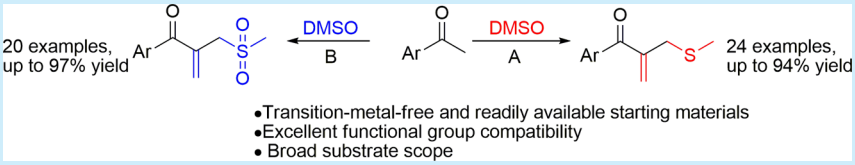
Acid Promoted Direct Cross-Coupling of Methyl Ketones with Dimethyl Sulfoxide: Access to Ketoallyl Methylsulfides and -sulfones

Zhen-Kang Wen,*[,†] Xue-Hua Liu,[†] Yu-Fang Liu,[†] and Jian-Bin Chao[‡]

[†]School of Chemistry and Chemical Engineering, Shanxi University, Taiyuan 030006, China

[‡]Scientific Instrument Center, Shanxi University, Taiyuan 030006, China

Supporting Information

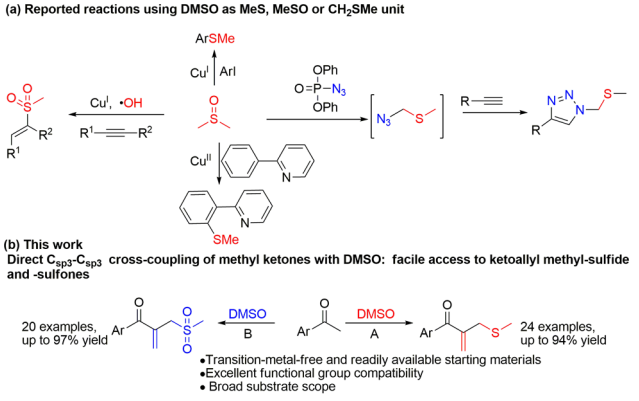


ABSTRACT: A new strategy to prepare β-acyl allylic methylsulfides and -sulfones through acid promoted direct cross-coupling of methyl ketones with dimethyl sulfoxide (DMSO) is reported. The reaction proceeded through the nucleophilic attack of enamine intermidiates derived from ketones to in situ generated thionium ion species, followed by elimination of methanthiol to give ketoallylic methylsulfides. With the prolonged reaction time, such products could be further reacted with a methyl sulfonyl radical, which might be generated from a methylthiosulfonate species, to afford ketoallylic methylsulfones in high yields. Molecular transformations of the allylic methylsulfides were also demonstrated.

Organosulfur compounds[1] have played an important role in organic chemistry and the drug discovery process owing to their unique properties and potential pharmaceutical applications. Notably, among the US top selling drugs in 2012, about 20% of the pharmaceuticals are organosulfur compounds.[2] During the past decades, many methods[1a−f,3] have been established for synthesis of organosulfur compounds, including Michael-type addition, nucleophilic substitution, and transition metal catalyzed C−H functionalizaiton. However, most of these methods need the use of odorous mercaptans, prefunctionalized substrates, and/or the requisite expensive transition metal catalysts. Therefore, exploration of novel and sustainable approaches that can access multifunctional organosulfur compounds from simple starting materials is still in great demand.

As a cheap and commercially available polar aprotic solvent, dimethyl sulfoxide (DMSO) has been widely used in organic synthesis owing to its rather low cost, relative stability, and low toxicity.[4] From a viewpoint of cost efficiency and step economy, it is considered to be one of the most ideal sulfur sources for assembly of the high-value organosulfur compounds. In this context, the Pummerer rearrangement[5] offers a straightforward protocol for construction of functionalized thioethers, in which DMSO served as an electrophilic $-CH_2SCH_3$ unit, while amides, azides, phenols, arenes, and alkenes could be employed as the nuclephiles.[6] Recently, transiton metal catalyzed introduction of a methylthio[7] (MeS−) or methylsulfinyl[8] (MeSO−) group into arenes or alkynes using DMSO was also documented (Scheme 1a). Despite these advances, all the above-mentioned carbon nucleophiles are thus far largely restricted to arenes, alkenes, or alkynes, whereas the direct functionalization of C(sp^3)−H bonds by installation of a sulfur-containing unit from DMSO has been rarely reported. This is presumably due to the C(sp^3) nucleophiles being incompatible with the electrophilic activation DMSO conditions, which resulted in a number of side reactions.[6] Inspired by a recent synergistic Pd/enamine strategy[9] for the direct functionalization of unactivated ketones, we envisaged that whether or not an enamine intermediate derived from a ketone could react with the activated DMSO, this would provide a promising chance to achieve direct cross-coupling of methyl ketones with DMSO. Herein, we report an unprecedented acid promoted direct cross-coupling reaction of methyl ketones with DMSO, which can access β-acyl allylic methylsulfides[10] and -sulfones in high yields (Scheme 1b). The reaction proceeded with excellent functional group compatibility and a broad

Scheme 1. Synthetic Application of DMSO as Sulfur Source



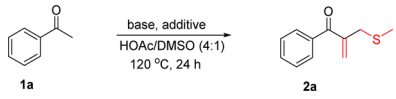
Received: September 4, 2017

DOI: 10.1021/acs.orglett.7b02753
Org. Lett. XXXX, XXX, XXX−XXX

substrate scope. Significantly, this protocol will undoubtedly provide a facile route to access valuable organosulfur compounds from simple starting materials.

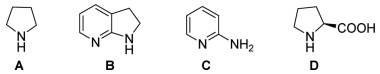
We commenced our study with acetophenone (**1a**) as the model substrate in DMSO/HOAc (4:1) at 120 °C. Interestingly, when pyrolidine (**A**) was employed to generate the enamine intermediate, ketoallylic methylsufide **2a** was formed in 54% yield (Table 1, entries 1−2). Further investigation showed that

Table 1. Optimization Reaction Conditions for the Coupling Reaction of Methyl Ketone with DMSO



entry[a]	base	additive	amine	yield[b] (%)
1	–	–	–	8
2	–	–	**A**	54
3	NaOAc	–	**A**	63
4	NaOAc	$TsOH{\cdot}H_2O$	**A**	74
5	LiOAc	$TsOH{\cdot}H_2O$	**A**	62
6	KOAc	$TsOH{\cdot}H_2O$	**A**	63
7	CsOAc	$TsOH{\cdot}H_2O$	**A**	65
8	NaOAc	$TsOH{\cdot}H_2O$	**B**	0
9	NaOAc	$TsOH{\cdot}H_2O$	**C**	0
10	NaOAc	$TsOH{\cdot}H_2O$	**D**	20
11[c]	NaOAc	$TsOH{\cdot}H_2O$	**A**	81

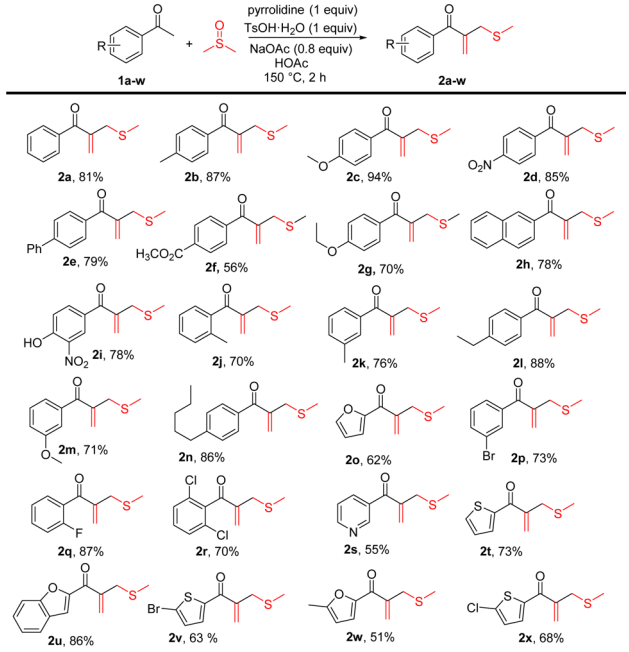
[a]Conditions: the reaction was conducted with acetophenone (0.25 mmol, 1 equiv), amine (0.25 mmol, 1 equiv), base (0.2 mmol, 0.8 equiv), additive (0.25 mmol, 1 equiv), solvent = HOAc/DMSO. [b]Isolated yield. [c]The reaction was run for 2 h at 150 °C.



using NaOAc as the base could increase the yield of **2a** (entry 3). We were pleased to find that the combination of NaOAc with $TsOH{\cdot}H_2O$ exhibited excellent reactivity, which afforded **2a** in 74% yield (entry 4), while other bases such as LiOAc, KOAc, and CsOAc delivered **2a** in slightly lower yields (entries 5−7). Other amines such as 2,3-dihydro-7-azaindole (**B**), 2-aminopyridine (**C**) and L-proline (**D**) instead of pyrolidine resulted in low yields or no reaction (entries 8−10). A brief examination of temperature revealed that **2a** could be isolated in 81% yield at 150 °C for 2 h (entry 11). Thus, the standard conditions were established as follows: the mixture of acetophenone (0.25 mmol), DMSO (0.5 mL), NaOAc (0.8 equiv), and $TsOH{\cdot}H_2O$ (1 equiv) in HOAc (2 mL) was stirred for 2 h at 150 °C.

With the optimized reaction conditions in hand, we examined the generality of this unique reaction for the synthesis of allylic sulfur substituted α,β-unsatrurated ketone products **2** from ketones **1** and DMSO. As shown in Chart 1, all reactions proceeded well to provide the corresponding products in good to excellent yields. Both electron-donating and -withdrawing group substituted aryl ketones efficiently reacted with DMSO in good to excellent yields (**2b-d**, **2f**, **2g**). Moreover, *ortho*-, *meta*-, and *para*-substituted aryl ketones were all tolerated and provided the desired products in high yields (**2j−n**). Various functional groups such as phenyl, F, Br, Cl, and free OH also yielded the corresponding products in high yields (**2e**, **2i**, **2p−r**). In addition, 2-naphthalene methyl ketone could react well and gave **2h** in good yield. Finally, efforts were taken to expand this protocol to other functionalized heteroaryl ketones such as pyridine, furan,

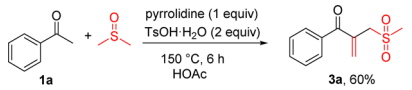
Chart 1. Substate Scope for the Reaction of Methyl Ketones with DMSO[a,b]



[a]Conditions: The reaction was conducted with acetophenone (0.25 mmol, 1 equiv), pyrrolidine (0.25 mmol, 1 equiv), NaOAc (0.2 mmol, 0.8 equiv), $TsOH{\cdot}H_2O$ (0.25 mmol, 1 equiv), solvent = HOAc (2 mL), and DMSO (0.5 mL), at 150 °C for 2 h, unless otherwise noted. [b]The yields indicated were determined upon isolation.

thiophene, and benzofuran; all these substrates were tolerated and afforded the desired products in high yields (**2o**, **2s−x**).

Remarkably, when **1a** was treated with 1 equiv of pyrrolidine in DMSO/HOAc (1:4) in the presence of 2 equiv of $TsOH{\cdot}H_2O$ as an additive at 150 °C for 6 h, an allylic sulfone product **3a** could be obtained in 60% yield (eq 1).[11] This result led us to develop another cascade process for the synthesis of allylic methysulfones.



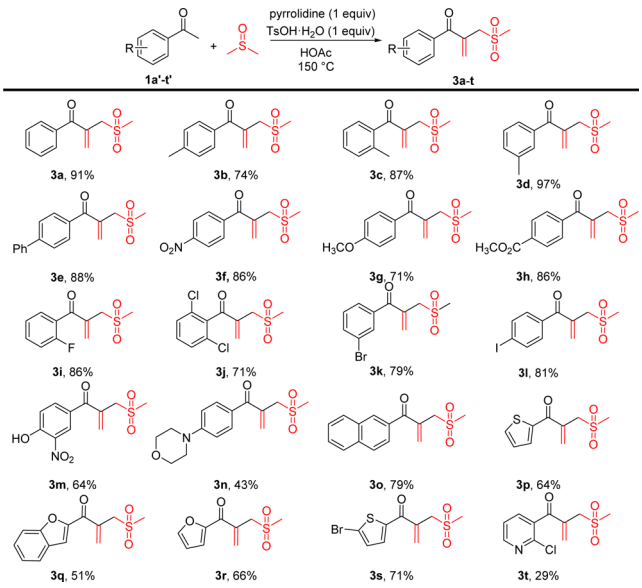
(1)

As depicted in Chart 2, all of the reactions worked well and gave the ketoallylic methylsulfone products in good to excellent yields. The substituents at different positions (*ortho*-, *meta*-, *para*-) on the phenyl ring of arylketones (**3b−d**) had no obvious influence on the yields. Both electron-withdrawing and -donating group functionalized arylketones afforded the corresponding ketoallylic methylsulfone products in good yields (**3e−h**). The current process also tolerates halogenated substrates (**3i−l**) especially the bromo and iodo group, which exhibited a variety of versatile synthetic handles in further elaboration. Notably, free hydroxyl and amine groups were compatible in this reaction and gave the desired products in moderate to good yields (**3m**, **3n**). Furthermore, other aryl and heteroaryl ketones, in particular, naphthalene-, thiophene-, benzofuran-, furan-, thiophene-, and pyridine-containing substrates (**3o−t**) were applicable to this process and afforded the corresponding products in reasonable yields.

To gain insight into the mechanism of the direct cross-coupling of methyl ketone with DMSO, several experiments

DOI: 10.1021/acs.orglett.7b02753
Org. Lett. XXXX, XXX, XXX−XXX

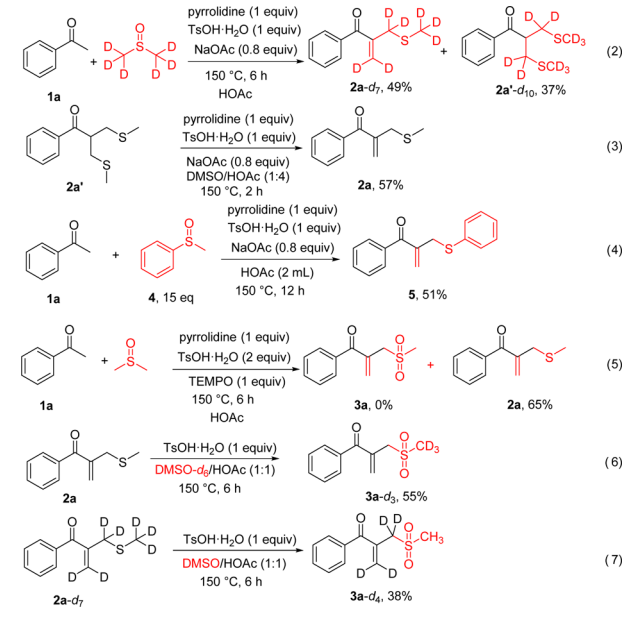
Chart 2. Substrate Scope for the Synthesis of Keto Allylic Methylsulfones[a,b]



[a]Conditions: The reaction was conducted with TsOH·H_2O (0.25 mmol, 1 equiv) in a mixed DMSO (0.5 mL) and acetic acid (0.5 mL) solvent heated at 150 °C for 10 h, and then acetophenone (0.25 mmol, 1 equiv) and pyrrolidine (0.25 mmol, 1 equiv) were added to the reaction mixture at 150 °C for 1 h, unless otherwise noted. [b]The yields indicated were determined upon isolation.

were performed (Scheme 2). Initially, the reaction of acetophenone (**1a**) with DMSO-d_6 under the standard reaction

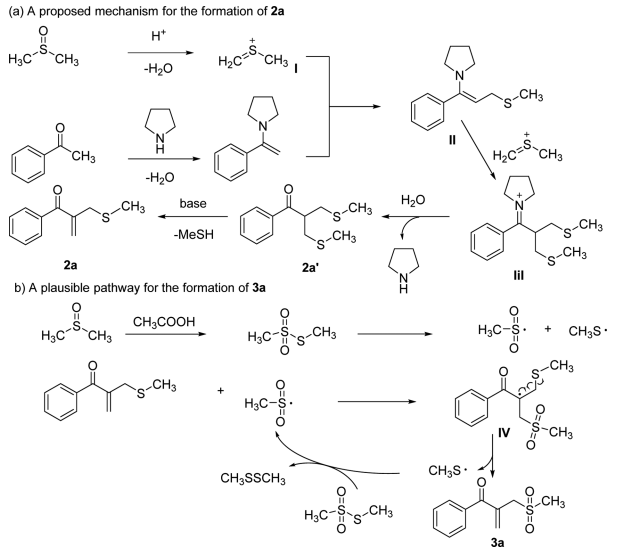
Scheme 2. Control Experiments for the Mechanism Study



conditions afforded the deuterated products **2a**-d_7 and **2a**′-d_{10} in 49% and 37% yields, respectively (eq 2), which suggested that DMSO may behave as a source of the CH_2SCH_3 unit. Furthermore, **2a**′ could be converted to ketoallylic methylsulfide **2a** (eq 3) under the standard reaction conditions, confirming that **2a**′ was the key intermediate in this reaction process. Other sulfoxides such as phenyl methyl sulfoxide could be used as a sulfur source in this transformation with good efficiency (eq 4). Moreover, when TEMPO was added in the reaction conditions to prepare ketoallylic methylsulfones, only ketoallylic methylsulfide **2a** was obtained and no ketoallylic methylsulfone **3a** was observed (eq 5), which indicated that the allylic methylsulfone could be formed through a radical pathway. In addition, the successful transformations of **2a** to **3a**-d_3, **2a**-d_7 to **3a**-d_4 (eqs 6 and 7) revealed that such transformations proceeded through the addition of a $MeSO_2$ unit to the double bond of **2a** along with the elimination of a methylthio group (−MeS). These control experiments suggested that the allylic methylsulfide **2a** was the key intermediate in the formation of allylic methylsulfone **3a**.

Based on these observation, a plausible mechanism of present transformation was proposed as shown in Scheme 3. Initially,

Scheme 3. Proposed Mechanism for the Reaction of Methyl Keones with DMSO

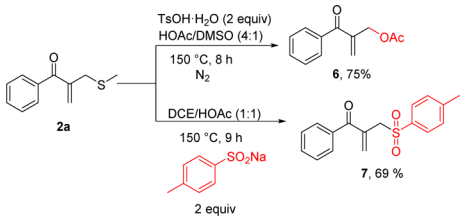


DMSO was activated by acid to generate a reactive electrophilic thionium ion **I**,[5e,12] which was attacked by the enamine intermediate derived from ketone **1a** to give the bisalkylsulfurized intermediate **III**. The following hydrolysis and elimination of MeSH provided the ketoallylic methylsufide **2a**. On the other hand, it has been reported that a methyl sulfonyl radical ($MeSO_2$) could be generated via homolysis of the S−S bond of a methylthiosulfonate, which was generated from the reaction of DMSO with acetic acid in the presence of TsOH.[13] With a prolonged reaction time, such $MeSO_2$ underwent addition to the double bond of the resulted allylic methylsulfide **2a**, leading to allylic methylsulfone product **3a** along with the release of a methyl mercaptan radical. This radical in turn reacted with methylthiosulfonate to regenerate $MeSO_2$ with the propagation of the radical chain.

Allyllic methylsulfides as well as allylic sulfones are very important and quite useful building blocks in organic synthesis.[14] Therefore, further organic transformations were conducted to demonstrate the utility of the allylic methylsulfide products (Scheme 4). Treatment of **2a** with TsOH·H_2O in DMSO/HOAc under N_2 for 8 h gave the allylic acetate product **6** in 75% yield. Furthermore, the combination of **2a** with 2 equiv sodium *p*-toluenesulfinate in DCE/HOAc (1:1) at 150 °C for 9 h afforded the allylic *p*-toluenesulfonylated product **7** in high yield.

DOI: 10.1021/acs.orglett.7b02753
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Transformations of the Ketoallylic Methylsufide



In summary, we have developed a novel acid-promoted direct cross-coupling reaction of methyl ketones and DMSO to prepare *β*-acyl allylic methylsulfides and sulfones. High yields and wide functional group tolerance were observed. The resulting sulfur-containing compounds could be transformed to useful organic synthons. We expect that these controllable processes will provide new routes to access functionalized ketoallylic sulfides and sulfones with versatile uses in synthetic and medicinal applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02753.

Experimental procedures, product characterizations (^{1}H NMR, ^{13}C NMR, HRMS), and copies of the ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zkwen@sxu.edu.cn.

ORCID

Zhen-Kang Wen: 0000-0003-1253-9583

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (21502106) and the National Natural Science Foundation for Young Scientists of Shanxi Province (201701D221028). We thank Prof. Yunhe Xu (USTC, China) and Prof. Yifeng Wang (USTC, China) for valuable discussions. We are also very grateful for the test platform provided by Scientific Instrument Center of Shanxi University.

■ REFERENCES

(1) (a) Koschker, P.; Breit, B. *Acc. Chem. Res.* **2016**, *49*, 1524. (b) Castarlenas, R.; Di Giuseppe, A.; Pérez-Torrente, J. J.; Oro, L. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 211. (c) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (d) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133. (e) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239. (f) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205. (g) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832. (h) *Sulphur-Containing Durgs and Related Organic Compounds*; Damani, L. A., Ed.; Wiley: New York, 1989.

(2) (a) Gómez, J. E.; Guo, W. S.; Kleij, A. W. *Org. Lett.* **2016**, *18*, 6042. (b) Gao, W. C.; Lv, H.; Zhang, X. M. *Org. Lett.* **2017**, *19*, 2877.

(3) For reviews, see: (a) Shen, C.; Zhang, P. F.; Sun, Q.; Bai, S. Q.; Hor, T. S. A.; Liu, X. G. *Chem. Soc. Rev.* **2015**, *44*, 291. (b) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev.* **2014**, *114*, 8807. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. For recent corresponding examples, see: (d) Deeming, A. S.; Russell, C. J.; Willis, M. C. *Angew. Chem., Int. Ed.* **2016**, *55*, 747. (e) Huang, Z. Y.; Lu, Q. Q.; Liu, Y. C.; Liu, D.; Zhang, J.; Lei, A. W. *Org. Lett.* **2016**, *18*, 3940. (f) Sun, F.-G.; Li, M.; He, C.-F.; Wang, B.; Li, B.; Sui, X. W.; Gu, Z. H. *J. Am. Chem. Soc.* **2016**, *138*, 7456. (g) Li, Y. Y.; Qiu, D. C.; Gu, R. R.; Wang, J. L.; Shi, J. R.; Li, Y. *J. Am. Chem. Soc.* **2016**, *138*, 10814. (h) Mukherjee, S.; Maji, B.; Tlahuext-Aca, A.; Glorius, F. *J. Am. Chem. Soc.* **2016**, *138*, 16200. (i) Chen, J. A.; Meng, S. X.; Wang, L. M.; Tang, H. M.; Huang, Y. *Chem. Sci.* **2015**, *6*, 4184.

(4) (a) Wu, X. F.; Natte, K. *Adv. Synth. Catal.* **2016**, *358*, 336. (b) Jones-Mensah, E.; Karki, M.; Magolan, J. *Synthesis* **2016**, *48*, 1421. (c) Soroko, I.; Bhole, Y.; Livingston, A. G. *Green Chem.* **2011**, *13*, 162.

(5) For selected recent reviews, see: (a) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5832. (b) Akai, S.; Kita, Y. *Top. Curr. Chem.* **2007**, *274*, 35. (c) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401.

(6) For selected recent examples of intermolecular Pummerer reactions, see: (a) Shen, T.; Huang, X. Q.; Liang, Y. F.; Jiao, N. *Org. Lett.* **2015**, *17*, 6186. (b) Hu, G.; Xu, J. X.; Li, P. F. *Org. Lett.* **2014**, *16*, 6036. (c) Abe, T.; Ikeda, T.; Itoh, T.; Hatae, N.; Toyota, E.; Ishikura, M. *Heterocycles* **2014**, *88*, 187. (d) Liu, J.; Wang, X.; Guo, H.; Shi, X.; Ren, X.; Huang, G. *Tetrahedron* **2012**, *68*, 1560. (e) Laleu, B.; Machado, M.; Lacour, J. *Chem. Commun.* **2006**, 2786. (f) Akai, S.; Kawashita, N.; Satoh, H.; Wada, Y.; Kakiguchi, K.; Kuriwaki, I.; Kita, Y. *Org. Lett.* **2004**, *6*, 3793.

(7) (a) Sharma, P.; Rohilla, S.; Jain, N. *J. Org. Chem.* **2015**, *80*, 4116. (b) Liu, F. L.; Chen, J. R.; Zou, Y. Q.; Wei, Q.; Xiao, W. J. *Org. Lett.* **2014**, *16*, 3768. (c) Mal, K.; Sharma, A.; Maulik, P. R.; Das, I. *Chem. - Eur. J.* **2014**, *20*, 662. (d) Gao, Q. H.; Wu, X.; Li, Y. H.; Liu, S.; Meng, X. G.; Wu, A. X. *Adv. Synth. Catal.* **2014**, *356*, 2924. (e) Dai, C.; Xu, Z. Q.; Huang, F.; Yu, Z. K.; Gao, Y. F. *J. Org. Chem.* **2012**, *77*, 4414. (f) Luo, F.; Pan, C. D.; Li, L. P.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, *47*, 5304. (g) Chu, L. L.; Yue, X. Y.; Qing, F. L. *Org. Lett.* **2010**, *12*, 1644. (h) Yin, G. D.; Zhou, B. H.; Meng, X. G.; Wu, A. X.; Pan, Y. J. *Org. Lett.* **2006**, *8*, 2245.

(8) (a) Pramanik, M. M. D.; Rastogi, N. *Chem. Commun.* **2016**, *52*, 8557. (b) Gao, X. F.; Pan, X. J.; Gao, J.; Huang, H. W.; Yuan, G. Q.; Li, Y. W. *Chem. Commun.* **2015**, *51*, 210. (c) Jiang, Y. J.; Loh, T. P. *Chem. Sci.* **2014**, *5*, 4939. (d) Yuan, G. Q.; Zheng, J. H.; Gao, X. F.; Li, X. W.; Huang, L. B.; Chen, H. G.; Jiang, H. F. *Chem. Commun.* **2012**, *48*, 7513.

(9) (a) Xu, Y.; Su, T. S.; Huang, Z. X.; Dong, G. B. *Angew. Chem., Int. Ed.* **2016**, *55*, 2559. (b) Yang, C.; Zhang, K. F.; Wu, Z. J.; Yao, H. Q.; Lin, A. J. *Org. Lett.* **2016**, *18*, 5332. (c) Liu, R. R.; Li, B. L.; Lu, J.; Shen, C.; Gao, J. R.; Jia, Y. X. *J. Am. Chem. Soc.* **2016**, *138*, 5198. (d) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065. (e) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336.

(10) During our preparation of this manuscript, a $K_2S_2O_8$ mediated coupling reaction between methyl ketones with dimethyl sulfoxide to prepare *β*-methylthio isopropenylketones was reported; see: Liu, Y. F.; Zhan, X.; Ji, P. Y.; Xu, J. W.; Liu, Q.; Luo, W. P.; Chen, T. Q.; Guo, C. C. *Chem. Commun.* **2017**, *53*, 5346.

(11) We also isolated a methylthiosulfonate byproduct in this process; further exploration suggested that an in situ generated methylthiosulfonate intermediate was critical to the allylic sulfone synthesis.

(12) (a) Jiang, X.; Wang, C.; Wei, Y. W.; Xue, D.; Liu, Z. T.; Xiao, J. L. *Chem. - Eur. J.* **2014**, *20*, 58. (b) Padwa, A.; Bur, S. K.; Danca, D. M.; Ginn, J. D.; Lynch, S. M. *Synlett* **2002**, *2002*, 851.

(13) Freeman, F.; Angeletakis, C. N. *J. Am. Chem. Soc.* **1983**, *105*, 4039.

(14) (a) Pritzius, A. B.; Breit, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 3121. (b) Pritzius, A. B.; Breit, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 15818. (c) Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8652. (d) Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 4568. (e) Liu, T.; Zhao, X.; Lu, L.; Cohen, T. *Org. Lett.* **2009**, *11*, 4576. (f) Lin, Y. A.; Chalker, J. M.; Floyd, N.; Bernardes, G. J. L.; Davis, B. G. *J. Am. Chem. Soc.* **2008**, *130*, 9642. (g) Chen, X.; Hussain, S.; Parveen, S.; Zhang, S.; Yang, Y.; Zhu, C. *Curr. Med. Chem.* **2012**, *19*, 3578. (h) Pfisterer, A.; Eisele, K.; Chen, X.; Wagner, M.; Müllen, K.; Weil, T. J. *Chem. - Eur. J.* **2011**, *17*, 9697. (i) Alba, A. N. R.; Companyó, X.; Rios, R. *Chem. Soc. Rev.* **2010**, *39*, 2018. (j) El-Awa, A.; Noshi, M. N.; Mollat du Jourdin, X.; Fuchs, P. L. *Chem. Rev.* **2009**, *109*, 2315.

DOI: 10.1021/acs.orglett.7b02753
Org. Lett. XXXX, XXX, XXX−XXX