JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

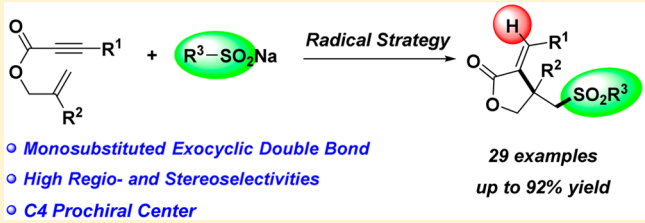
Synthesis of Sulfonylated Lactones via Ag-Catalyzed Cascade Sulfonylation/Cyclization of 1,6-Enynes with Sodium Sulfinates

Wanqing Wu,* Songjian Yi, Yue Yu, Wei Huang, and Huanfeng Jiang*

Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China

Supporting Information

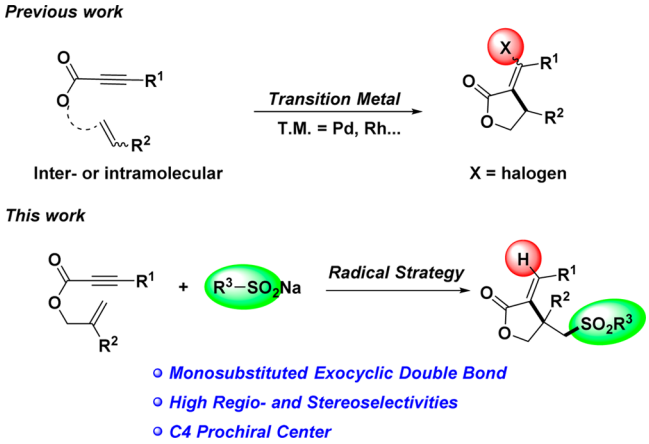
ABSTRACT: A novel strategy for the synthesis of sulfonylated lactones via Ag-catalyzed radical addition/cyclization reaction of 1,6-enynes and sodium sulfinates has been developed. The reaction presents high stereoselectivity under mild conditions with C4 prochiral center construction in one step. The ESR experiments and relevant mechanistic studies indicated that a radical pathway should be involved in this transformation.



There has been growing interest in the rational design of drug-framework molecules through the introduction of different kinds of special functional groups.[1] Owing to the distinctive structure and electronic features, the sulfonyl group is one of the most important members of this family, which has been extensively exploited in medicinal chemistry and agrochemical industry.[2] In view of these applications, several elegant methods for incorporating the sulfonyl group into organic molecules by transition-metal-catalyzed[3] as well as free radical-mediated[4] pathways have been established. Nevertheless, the scope of sulfonyl substrates was usually limited and the reaction conditions were relatively harsh. Therefore, the development of versatile and efficient methods for constructing different useful skeletons bearing sulfonyl group is highly desirable.

In addition, α-methylene-γ-butyrolactones are ubiquitous subunits in a wide variety of sesquiterpene, which are known to possess significant biological activities.[5] The exocyclic double bond not only is considered to be responsible for the interesting biological properties of γ-lactones but also serves as a functional group for further manipulations in organic synthesis.[6] The development of methods facilitating the synthesis of γ-lactones has attracted attention from many research groups due to their intriguing biological activities and their potential as synthetic intermediates.[7,8] For example, Zhang's group has reported the Rh-catalyzed oxidative cyclization of the enyne substrates to construct the γ-lactone products.[7d] Recently, a Pd-catalyzed intermolecular carboesterification of alkenes with alkynes for the synthesis of α-methylene-γ-butyrolactones has been developed by our group.[9a] However, most of these methods required prefunctionalized precursors or noble transition metals, which generated the halo-substituted double bond products. Besides, to the best of our knowledge, the introduction of sulfone groups into the unique lactone skeleton is still less explored. As part of our continuing program on γ-lactone synthesis[9] and sulfonylation reactions,[10] herein, we disclose a convenient and concise method for the construction of diverse sulfonylated lactones by using sulfinate sodium as the key starting material and $AgNO_3$ as the catalyst in a one-pot manner.[11] This method provides an efficient entry to the monosubstituted alkene lactone products with a C4 prochiral center, which should find potential applications in natural product synthesis and medicinal chemistry (Scheme 1).

Scheme 1. Methods for Sulfonylated γ-Lactones

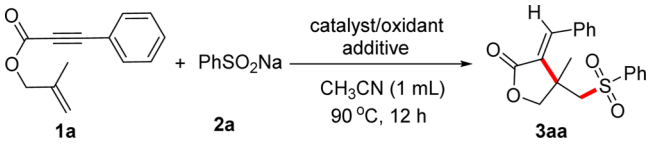


Initially, we chose 2-methylallyl 3-phenylpropiolate (**1a**) and sodium benzensulfinate (**2a**) as the model substrates for optimization of the conditions (Table 1). As expected, when **1a** was treated with **2a** in the presence of 10 mol % of $AgNO_3$ and $K_2S_2O_8$ as the oxidant at 90 °C for 12 h, the desired sulfonylated lactone **3aa** was detected in 40% GC yield (Table 1, entry 1). And the molecular structure of **3aa** was unambiguously determined by X-ray crystallographic analysis

Received: October 4, 2016
Published: December 28, 2016

DOI: 10.1021/acs.joc.6b02416
J. Org. Chem. 2017, 82, 1224−1230

Table 1. Optimization of Reaction Conditions[a]



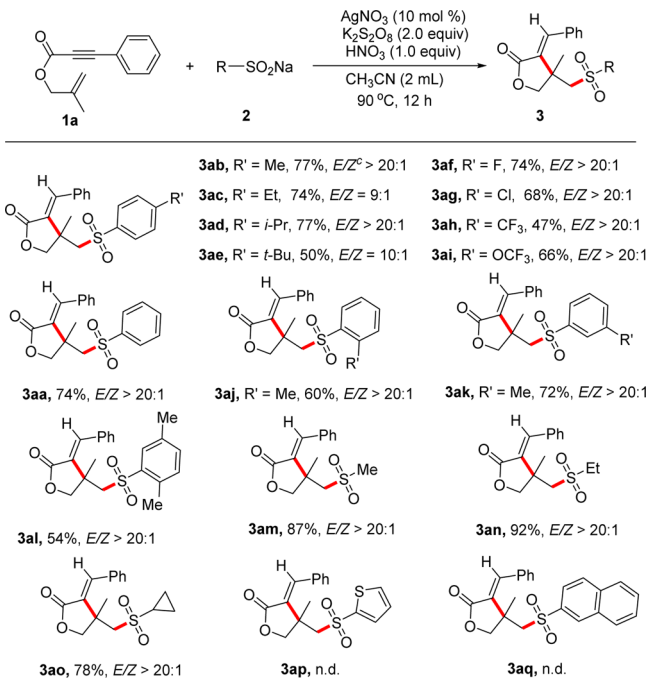
entry[a]	catalyst	oxidant	additive	yield (%)[b]
1	$AgNO_3$	$K_2S_2O_8$	–	40
2	$AgNO_3$	TBHP	–	N.R.
3	$AgNO_3$	CuO	–	N.D.
4	$AgNO_3$	DDQ	–	N.R.
5	$AgNO_3$	$PhI(OAc)_2$	–	N.R.
6	Ag_2O	$K_2S_2O_8$	–	25
7	$AgCO_3$	$K_2S_2O_8$	–	34
8	Ag	$K_2S_2O_8$	–	22
9	$AgNO_3$	$K_2S_2O_8$	$Fe(NO_3)_3$	trace
10	$AgNO_3$	$K_2S_2O_8$	$Ca(NO_3)_2$	trace
11	$AgNO_3$	$K_2S_2O_8$	$Mg(NO_3)_2·6H_2O$	9
12	$AgNO_3$	$K_2S_2O_8$	$Cu(NO_3)_2·3H_2O$	14
13	$AgNO_3$	$K_2S_2O_8$	$Zn(NO_3)_2·6H_2O$	58
14	$AgNO_3$	$K_2S_2O_8$	HNO_3 (4.0 equiv)	34
15	**$AgNO_3$**	**$K_2S_2O_8$**	**HNO_3 (1.0 equiv)**	**74**
16	–	$K_2S_2O_8$	HNO_3 (1.0 equiv)	23

[a]Reaction conditions: All reactions were performed with **1a** (0.1 mmol), **2a** (2.0 equiv), catalyst (10 mol %), additive (2.0 equiv), 1.0 mL of solvent at 90 °C for 12 h unless otherwise noted. N.R. = no reaction. N.D. = not detected. [b]Determined by GC-MS.

(see the Supporting Information for details).[12] Subsequent survey on a series of representative oxidants revealed that $K_2S_2O_8$ gave the best result; however, TBHP, CuO, DDQ, or $PhI(OAc)_2$ was not suitable for this reaction (Table 1, entries 2−5). These results suggested that both Ag(0) and Ag(I) were efficient for this cyclization reaction, although the yields were not enhanced obviously (Table 1, entries 6−8). According to the literature,[13] we supposed that the nitrates or diluted nitric acid might have an acceleration effect on this reaction, and different nitrates as well as diluted nitric acid were screened for this transformation. When 2.0 equiv of $Zn(NO_3)_2·6H_2O$ were used as an additive, the desired product **3aa** was obtained in 58% yield (Table 1, entry 13). Pleasingly, when 1.0 equiv of HNO_3 was added into the reaction, the yield of **3aa** was improved to 74% (Table 1, entry 15). Control experiments indicated that the product yield declined obviously in the absence of the Ag catalyst (Table 1, entry 16). Additionally, when lowering the reaction temperature, the yield of **3aa** declined dramatically. Thus, the optimized reaction conditions were affirmed as follows: 10 mol % $AgNO_3$ as the catalyst, 2.0 equiv of $K_2S_2O_8$, and 1.0 eqiuv of HNO_3 as the additive in CH_3CN at 90 °C for 12 h.

With the optimized conditions in hand, the substrate scope of sodium sulfinates was examined. As shown in Table 2, the reactions of sodium benzensulfinates bearing both electron-donating (e.g., Me, *t*-Bu) and electron-withdrawing groups (e.g., F, CF_3) at the *para*-position on the aryl ring worked well under the optimal conditions and afforded the corresponding γ-lactones **3aa**−**3ai** in moderate yields. In most cases, excellent *Z*/*E* ratios were obtained, which were determined by ^1H NMR analysis. *Meta*- and *ortho*-substituents on the phenyl ring were well tolerated under this condition (**3aj**, **3ak**). The transformation of a disubstituted substrate also proceeded well to give the desired product **3al**. To our delight, the alkyl sodium

Table 2. Reactions of 1a with Different Sodium Sulfinates 2[a,b]



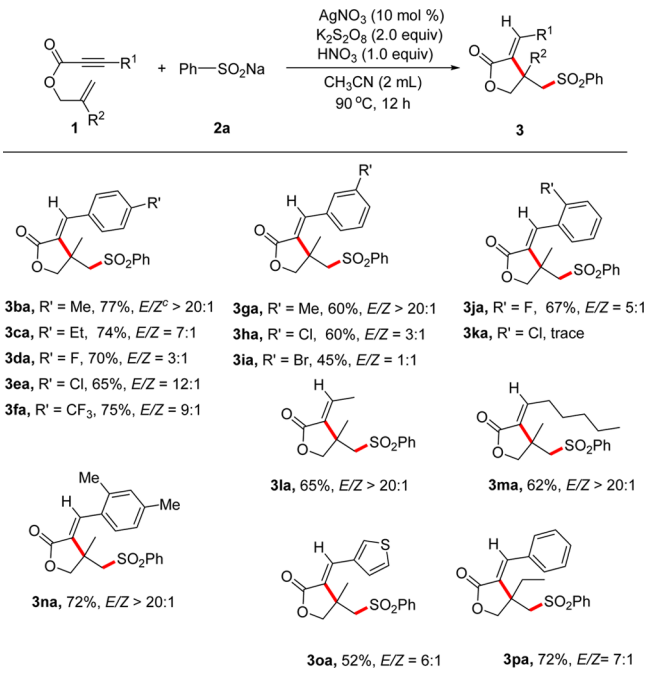
[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), $AgNO_3$ (10 mol %), $K_2S_2O_8$ (2 equiv) and HNO_3 (0.4 M, 0.25 mL) in 2 mL CH_3CN at 90 °C for 12 h unless otherwise noted. n.d. = not detected. [b]Determined by GC-MS. [c]The ratio of *E*/*Z* was determined by ^1H NMR analysis.

sulfinates, such as methyl, ethyl, and cyclopropyl were compatible with this protocol and transferred to the corresponding products **3am**−**3ao** in good to excellent yields. However, the reactions of heterocyclic substituted sodium sulfinates failed to provide the desired products under the current catalytic conditions (**3ap** and **3aq**).

After successfully investigating the range of sodium sulfinates, we next evaluated the scope of 1,6-enynes. As depicted in Table 3, for the *para*-position of phenyl ring, the reactions with electron-withdrawing groups (e.g., F, CF_3) provided similar yields to those with electron-donating groups (e.g., Me, Et). Interestingly, the reaction of 2-methylallyl 3-(4-(trifluoromethyl)phenyl) propiolate gave **3fa** in 75% yield. Moreover, the 1,6-enynes with a *meta*-position substituent were found to be suitable for this reaction and transferred to the corresponding products **3ga**−**3ia** in moderate yields. It was worth noting that 2-F substitution on the phenyl ring provided the better yield (67%) than that with 2-Cl substitution. The dependence of the yield upon substitution partners likely relied on the corresponding steric hindrance. When R^1 underwent alkyl substitution, the reaction proceeded smoothly to provide the target products **3la** and **3ma** in 65% and 62% yields, respectively. In addition, the heterocyclic group, such as thienyl, attached to the triple bond was also compatible with the reaction conditions, affording the desired lactone product **3oa** in moderate yield. The substrate with germinal substituents could be converted to the corresponding product **3na** in 72% yield. When a substituted allylic enyne substrate was applied to the standard conditions, product **3pa** was isolated in 72% yield, whereas no reaction occurred in the case of unsubstituted olefin

DOI: 10.1021/acs.joc.6b02416
J. Org. Chem. 2017, 82, 1224−1230

Table 3. Reactions of Different 1,6-Enynes 1 with 2a[a,b]

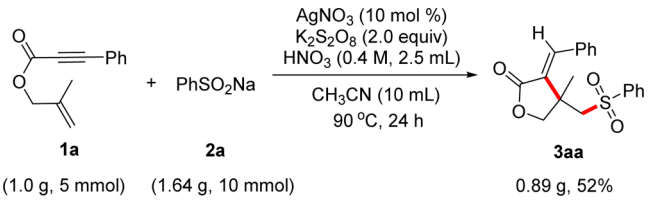


[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), $AgNO_3$ (10 mol %), $K_2S_2O_8$ (2 equiv) and HNO_3 (0.4 M, 0.25 mL) in 2 mL of CH_3CN at 90 °C for 12 h unless otherwise noted. [b]Determined by GC-MS. [c]The ratio of *E*/*Z* was determined by ^1H NMR analysis.

(R^2 = H), indicating that the substituents in the internal position of the alkene affected the yield dramatically.

Furthermore, the reaction is scalable and practical since a synthetically useful yield (52%) of the sulfonylated lactone product was obtained when the reaction was performed on 5 mmol scale (Scheme 2).

Scheme 2. Gram-Scale of the Reaction



To gain more insight into the mechanism of this reaction, several control experiments were performed (see the Supporting Information for details). First, when the radical scavenger TEMPO (2 equiv) or BHT (2 equiv) was added under the standard conditions, the yield of product **3aa** declined obviously, indicating the transformation should proceed via a free-radical pathway. The electron spin resonance (ESR) experiments were further conducted to support the sulfonyl radical intermediate.[14] An isotopic labeling study with D_2O was then performed and the kinetic isotope effect radio of **3am**/**3am-*d*** was 0.42, which suggested that the source of hydrogen might come from HNO_3 or H_2O. Moreover, an observation from a pH experiment was consistent with our assumption. The value increased from 0.40 to 0.61, suggesting that the diluted nitric acid could stimulate the last step of hydrolysis and enhance the product yield. It should be noted that when using the complex $PhSO_2Ag$ (**A**) as the catalyst, the reaction proceeded smoothly and afforded the lactone product in 51% yield, which proved that **A** should be the key intermediate in this process.

Base on the above results and previous reports, a possible mechanism for this transformation was proposed in Scheme 3. First, complex **A** is formed from sodium sulfinate and $AgNO_3$, which is supposed to be the key step in this transformation. When **A** is generated, it may undergo Path A involving silver-promoted generation of the sulfonyl radical **B** (Scheme 3, Path A), which subsequently adds to **1a** to give the alkyl radical **D**. Another possibility for the formation of the alkyl radical **D** is the addition of **A** to **1a**, providing the silver(I) species **C**, followed by the oxidation to form the alkyl radical **D** (Scheme 3, Path B). The resulting alkyl radical **D** then undergoes an intramolecular radical addition and cyclization reaction to afford the intermediate **E**. Finally, there may be a SET process to **E** from Ag(0) to Ag(I) and then give a vinyl anion **H**, which was subsequently protonated by HNO_3 or H_2O to give the desired product **3aa**. The model reaction was also monitored by a mass spectrometry experiment (see the Supporting Information for details). It is worth noting that the ESI-MS shows peaks at *m*/*z* 304.9914 and *m*/*z* 705.1578, which correspond to $[G + H]^+$ and $[F + H]^+$, respectively. These signals suggested that the sulfonyl radical was formed during the reaction, which strongly supported our hypothesis that a radical pathway should be involved in this chemical process.

In conclusion, we have established a highly efficient protocol for the synthesis of various sulfonylated lactones via Ag-catalyzed radical cascade sulfonylation/cyclization of 1,6-enynes with sodium sulfinates, which would be useful in organic synthesis and medicinal chemistry. With the green sodium sulfinate and $AgNO_3$ catalyst, this reaction shows high efficiency and selectivity, as well as a broad substrate scope. The exocyclic monosubstituted double bond and C4 prochiral center also make the present protocol very attractive, which will find potential applications in the synthesis of more complex and significant pharmaceuticals.[15]

EXPERIMENTAL SECTION

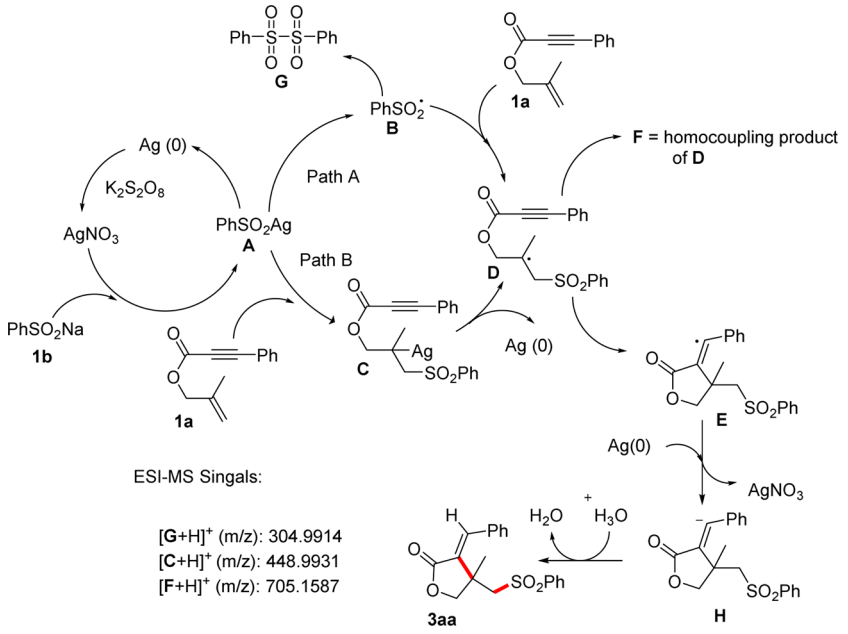
General Information. Melting points were measured with a melting point instrument and were uncorrected. ^1H and ^{13}C NMR spectra were recorded using a 400/600 MHz NMR spectrometer. The chemical shifts are referenced to signals at 7.26 and 77.0 ppm, respectively, and $CDCl_3$ is solvent. IR spectra were recorded on an FT-IR spectrometer using KBr discs. Melting points were taken on an electrothermal melting point apparatus and without correction. GC−MS was obtained using electron ionization. HRMS was obtained with an LCMS-IT-TOF mass spectrometer. TLC was performed by using commercially prepared 100−400 mesh silica gel plates, and visualization was effected at 254 nm.

*General Procedure for the Preparation of 1,6-Enyne Derivatives (**1**).* To a mixture of propiolic acid (10.0 equiv) and allyl alcohol (1.2 equiv) in CH_2Cl_2 (5 mL) was added a solution of DMAP (10 mol %) and DCC (1.5 equiv) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred for 10 h at 25 °C and filtered through a short plug of silica gel, which was rinsed with hexanes/EtOAc = 2/1. The filtrate was concentrated in vacuum, and the residue was purified by column chromatography on silica gel (hexanes/EtOAc = 10/1) to give **1**.

*General Procedure for the Preparation of Sodium Sulfinate Derivatives (**2**).* To a mixture of sodium bicarbonate (2.0 equiv) and sodium sulfite (2.0 equiv) in H_2O was added sulfonyl chloride (5 mmol) at room temperature. The reaction mixture was stirred for 10 h at 80 °C and then cooled down to room temperature. Excess H_2SO_4 was added to make the solution reach pH = 1 followed by extraction with ethyl acetate (3 × 20 mL). The combined organic layer was removed under vacuum, and then about 10 mL of H_2O were added to

DOI: 10.1021/acs.joc.6b02416
J. Org. Chem. 2017, 82, 1224−1230

Scheme 3. Tentative Mechanism



dissolve the solid. The solvent was basified with aqueous NaOH to reach pH = 8 and was removed under vacuum to afford the sodium sulfinates **2**.

*General Procedure for the Preparation of Sulfonylated γ-Lactones (**3**).* A dried Schlenk tube was charged with 1,6-enynes **1** (0.5 mmol, 1.0 equiv), sodium sulfinates **2** (1.0 mmol, 2.0 equiv), $AgNO_3$ (0.05 mmol, 0.1 equiv), $K_2S_2O_8$ (1.0 mmol, 2.0 equiv), HNO_3 (0.4 M, 0.25 mL), and CH_3CN (2 mL), which was equipped with a magnetic stirring bar. The mixture was stirred for 12 h at 80−90 °C. After the reaction was completed, saturated $NaHCO_3$ solvent (2 mL) was added to stop the reaction, and then ethyl acetate (3 × 5 mL) was added into the tube. The combined organic layers were washed with brine to neutral, dried over $MgSO_4$, and concentrated in vacuum. Purification of the residue on a preparative TLC afforded the desired products **3**.

*(E)-3-Benzylidene-4-methyl-4-((phenylsulfonyl)methyl)dihydrofuran-2(3H)-one (**3aa**).* Yellow solid (131 mg, 77% yield), mp = 129.1−130.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (d, J = 7.8 Hz, 2H), 7.71 (s, 1H), 7.63 (t, J = 7.3 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.41−7.36 (m, 3H), 7.31−7.28 (m, 2H), 4.72 (d, J = 9.6 Hz, 1H), 4.29 (d, J = 9.6 Hz, 1H), 3.54 (d, J = 14.5 Hz, 1H), 3.17 (d, J = 14.5 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.6, 140.5, 139.7, 134.0, 133.2, 132.5, 129.5, 129.4, 129.1, 128.7, 127.4, 76.3, 60.8, 41.9, 24.6; IR (KBr) ν_{max} 3628, 3111, 2925, 1753, 1641, 1524, 1310, 1146 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{18}O_4SNa$ 365.0818; Found 365.0823.

*(E)-3-Benzylidene-4-methyl-4-(tosylmethyl)dihydrofuran-2(3H)-one (**3ab**).* Yellow solid (137 mg, 77% yield), mp = 134.2−135.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.70 (s, 1H), 7.62 (d, J = 7.7 Hz, 2H), 7.41−7.36 (m, 3H), 7.34−7.25 (m, 4H), 4.71 (d, J = 9.6 Hz, 1H), 4.28 (d, J = 9.6 Hz, 1H), 3.53 (d, J = 14.5 Hz, 1H), 3.15 (d, J = 14.5 Hz, 1H), 2.42 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.7, 145.1, 139.6, 137.6, 133.2, 132.5, 129.9, 129.5, 129.2, 128.7, 127.4, 76.3, 60.9, 41.9, 24.5, 21.6; IR (KBr) ν_{max} 3685, 3114, 2982, 1753, 1639, 1526, 1309, 1143 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{20}O_4SNa$ 379.0975; Found 379.0973.

*3-Benzylidene-4-(((4-ethylphenyl)sulfonyl)methyl)-4-methyldihydrofuran-2(3H)-one (**3ac**).* Yellow solid (136 mg, 74% yield), mp = 120.4−121.9 °C; ***E* isomer + *Z* isomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.71 (s, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.42−7.36 (m, 3H), 7.34−7.28 (m,4H), 4.73 (d, J = 9.6 Hz, 1H), 4.29 (d, J = 9.6 Hz, 1H), 3.55 (d, J = 14.5 Hz, 1H), 3.17 (d, J = 14.5 Hz, 1H), 2.72 (q, J = 7.4 Hz, 2H), 1.68 (s, 3H), 1.25 (t, J = 7.3 Hz, 3H); ***E* isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.6, 151.3, 139.7, 137.9, 133.3, 132.6, 129.6, 129.3, 129.0, 128.9, 128.8, 127.6, 76.4, 61.0, 42.0, 289, 24.5, 15.1; IR (KBr) ν_{max} 3690, 3117, 2981, 2756, 1755, 1641, 1525, 1478, 1144 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{21}H_{22}O_4SNa$ 393.1131; Found 393.1134.

*(E)-3-Benzylidene-4-(((4-isopropylphenyl)sulfonyl)methyl)-4-methyldihydrofuran-2(3H)-one (**3ad**).* Yellow solid (147 mg, 77% yield), mp = 112.1−113.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.70 (s, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.42−7.36 (m, 3H), 7.36 (d, J = 8.1 Hz, 2H), 7.32−7.28 (m, 2H), 4.73 (d, J = 9.6 Hz, 1H), 4.28 (d, J = 9.6 Hz, 1H), 3.54 (d, J = 14.5 Hz, 1H), 3.17 (d, J = 14.5 Hz, 1H), 2.97 (dt, J = 13.5, 6.8 Hz, 1H), 1.68 (s, 3H), 1.25 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.7, 155.8, 139.6, 137.9, 133.2, 132.5, 129.5, 129.2, 128.7, 127.6, 127.5, 76.3, 60.9, 41.9, 34.2, 24.4, 23.5; IR (KBr) ν_{max} 3692, 3117, 2978, 2753, 1756, 1640, 1525, 1478, 1311, 1145 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{22}H_{24}O_4SNa$ 407.1288; Found 407.1286.

*3-Benzylidene-4-(((4-(tert-butyl)phenyl)sulfonyl)methyl)-4-methyldihydrofuran-2(3H)-one (**3ae**).* Yellow solid (99 mg, 50% yield), mp = 123.5−124.1 °C; ***E* isomer + *Z* isomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.68−7.65 (m, 2H), 7.63 (s, 1H), 7.49−7.47 (m, 2H), 7.37−7.33 (m, 3H), 7.29−7.28 (m, 2H), 4.72 (d, J = 9.6 Hz, 1H), 4.23 (d, J = 9.6 Hz, 1H), 3.52 (d, J = 14.6 Hz, 1H), 3.20 (d, J = 14.6 Hz, 1H), 1.62 (s, 3H), 1.27 (s, 9H); ***E* isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.6, 157.9, 139.5, 137.3, 133.0, 132.3, 129.3, 129.1, 128.5, 127.1, 126.2, 76.1, 60.7, 41.6, 35.0, 30.7, 24.4; IR (KBr) ν_{max} 3686, 3115, 2971, 2757, 1756, 1639, 1549, 1478, 1312, 1147 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{23}H_{26}O_4SNa$ 421.1444; Found 421.1447.

*(E)-3-Benzylidene-4-(((4-fluorophenyl)sulfonyl)methyl)-4-methyldihydrofuran-2(3H)-one (**3af**).* Yellow solid (133 mg; 74% yield), mp = 134.5−135.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.78−7.73 (m, 2H), 7.72 (s, 1H), 7.43−7.36 (m, 3H), 7.32−7.27 (m, 2H), 7.18 (t, J = 8.3 Hz, 2H), 4.73 (d, J = 9.6 Hz, 1H), 4.29 (d, J = 9.6 Hz, 1H), 3.50 (d, J = 14.5 Hz, 1H), 3.18 (d, J = 14.4 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.6, 165.9 (d, J = 257.4 Hz), 139.8, 136.6 (d, J = 2.0 Hz), 133.3, 132.4, 130.4 (d, J = 9.7 Hz), 129.6, 129.2, 128.8, 116.8 (d, J = 22.7 Hz), 76.2, 61.1, 42.0, 24.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −102.45 (s); IR (KBr) ν_{max} 3692, 3114, 2984, 2766, 1754, 1639, 1525, 1480, 1320, 1144 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{17}FO_4SNa$ 383.0724; Found 383.0728.

*(E)-3-Benzylidene-4-(((4-chlorophenyl)sulfonyl)methyl)-4-methyldihydrofuran-2(3H)-one (**3ag**).* Yellow solid (139 mg, 74% yield), mp

DOI: 10.1021/acs.joc.6b02416
J. Org. Chem. 2017, 82, 1224−1230

= 132.5−133.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.72 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 7.42−7.38 (m, 3H), 7.32−7.28 (m, 2H), 4.73 (d, J = 9.6 Hz, 1H), 4.30 (d, J = 9.6 Hz, 1H), 3.51 (d, J = 14.5 Hz, 1H), 3.18 (d, J = 14.5 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 173.9, 140.9, 140.0, 138.9, 133.2, 132.3, 129.7, 129.6, 129.2, 128.9, 128.8, 76.2, 60.9, 41.9, 24.8; IR (KBr) ν_{max} 3691, 3110, 2983, 2766, 1755, 1634, 1526, 1478, 1321, 1145 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{17}ClO_4SNa$ 399.0428; Found 399.0430.

(E)-3-Benzylidene-4-methyl-4-(((4-(trifluoromethyl)phenyl)-sulfonyl)methyl)dihydrofuran-2(3H)-one (**3ah**). Yellow solid (96 mg, 47% yield), mp = 140.2−141.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.83 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.68 (s, 1H), 7.40−7.34 (m, 3H), 7.29−7.24 (s, 2H), 4.70 (d, J = 9.6 Hz, 1H), 4.27 (d, J = 9.6 Hz, 1H), 3.49 (d, J = 14.4 Hz, 1H), 3.17 (d, J = 14.4 Hz, 1H), 1.66 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4, 143.0, 140.0, 135.8 (q, J = 33.3 Hz), 133.2, 132.2, 129.7, 129.2, 128.8, 128.1, 126.6 (q, J = 3.5 Hz), 122.9 (q, J = 271.5 Hz), 76.2, 60.8, 41.9, 24.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −63.40 (s); IR (KBr) ν_{max} 3689, 3112, 2978, 2753, 1755, 1638, 1478, 1311, 1145 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{17}F_3O_4SNa$ 433.0692; Found 433.0695.

(E)-3-Benzylidene-4-methyl-4-(((4-(trifluoromethoxy)phenyl)-sulfonyl)methyl)dihydrofuran-2(3H)-one (**3ai**). Yellow oil (140 mg, 66% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.8 Hz, 2H), 7.71 (s, 1H), 7.42−7.36 (m, 3H), 7.33 (s, 1H), 7.32−7.28 (m, 3H), 4.74 (d, J = 9.6 Hz, 1H), 4.28 (d, J = 9.6 Hz, 1H), 3.51 (d, J = 14.5 Hz, 1H), 3.23 (d, J = 14.5 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170. 6, 153.1, 139.9, 138.6, 133.2, 132.2, 131.0, 130.0, 129.8, 129.6, 129.2, 128.7, 121.1, 76.2, 60.9, 41.9, 24.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.69 (s); IR (KBr) ν_{max} 3690, 3111, 2983, 2767, 1755, 1640, 1525, 1256, 1150 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{17}F_3O_5SNa$ 449.0641; Found 449.0644.

(E)-3-Benzylidene-4-methyl-4-((o-tolylsulfonyl)methyl)dihydrofuran-2(3H)-one (**3aj**). Yellow oil (106 mg, 60% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.92 (d, J = 7.9 Hz, 1H), 7.73 (s, 1H), 7.49 (t, J = 7.4 Hz, 1H), 7.41−7.39 (m, 3H), 7.38−7.29 (m, 3H), 7.27 (d, J = 3.5 Hz, 1H), 4.69 (d, J = 9.7 Hz, 1H), 4.38 (d, J = 9.7 Hz, 1H), 3.64 (d, J = 14.4 Hz, 1H), 3.07 (d, J = 14.4 Hz, 1H), 2.43 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.6, 139.6, 138.7, 137.5, 134.1, 133.4, 133.0, 132.8, 129.5, 129.3, 129.1, 128.8, 126.9, 76.8, 60.0, 42.1, 24.8, 20.1; IR (KBr) ν_{max} 3694, 3111, 2982, 2768, 1756, 1663, 1526, 1478, 1310, 1245, 1142 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{20}O_4SNa$ 379.0975; Found 379.0978.

(E)-3-Benzylidene-4-methyl-4-((m-tolylsulfonyl)methyl)dihydrofuran-2(3H)-one (**3ak**). Yellow oil (128 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.66 (s, 1H), 7.51−7.47 (m, 2H), 7.38−7.33 (m, 5H), 7.26−7.24 (m, 2H), 4.68 (d, J = 9.6 Hz, 1H), 4.23 (d, J = 9.6 Hz, 1H), 3.48 (d, J = 14.5 Hz, 1H), 3.11 (d, J = 14.5 Hz, 1H), 2.35 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.7, 140.4 139.8, 139.7, 134.7, 133.3, 132.5, 129.5, 129.3, 129.2, 128.7, 127.6, 124.5, 76.3, 60.8, 41.9, 24.6, 21.2; IR (KBr) ν_{max} 3691, 3112, 2984, 2769, 1753, 1635, 1525, 1478, 1308, 1241, 1140 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{20}O_4SNa$ 379.0975; Found 379.0976.

(E)-3-Benzylidene-4-(((2,5-dimethylphenyl)sulfonyl)methyl)-4-methyldihydrofuran-2(3H)-one (**3al**). Yellow solid (100 mg, 54% yield), mp = 107.02−108.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 2H), 7.35−7.32 (m, 3H), 7.24−7.22 (m, 2H), 7.20 (s, 1H), 7.06 (d, J = 7.6 Hz, 1H), 4.62 (d, J = 9.5 Hz, 1H), 4.30 (d, J = 9.5 Hz, 1H), 3.55 (d, J = 14.4 Hz, 1H), 2.98 (d, J = 14.4 Hz, 1H), 2.30 (s, 3H), 2.28 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.6, 139.5, 138.3, 136.9, 134.7, 134.2, 133.4, 133.0, 132.7, 130.9, 129.5, 129.0, 128.8, 76.7, 59.8, 42.0, 24.8, 20.7, 19.5; IR (KBr) ν_{max} 3694, 3112, 2983, 2758, 1754, 1637, 1527, 1481, 1307, 1248, 1139 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{21}H_{22}O_4SNa$ 393.1131; Found 393.1131.

(E)-3-Benzylidene-4-methyl-4-((methylsulfonyl)methyl)dihydrofuran-2(3H)-one (**3am**). White solid (121 mg, 87% yield), mp = 120.4−121.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.77 (s, 1H), 7.45−7.43 (m, 3H), 7.37−7.35 (m, 2H), 4.68 (d, J = 9.6 Hz, 1H), 4.27 (d, J = 9.6 Hz, 1H), 3.43 (d, J = 14.2 Hz, 1H), 3.14 (d, J = 14.2 Hz, 1H), 2.82 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.6, 139.7, 133.3, 132.7, 129.6, 129.0, 128.8, 76.0, 59.2, 43.7, 41.6, 24.6; IR (KBr) ν_{max} 3692, 3113, 2984, 2767, 1752, 1631, 1525, 1479, 1307, 1242, 1138 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{14}H_{16}O_4SNa$ 303.0662; Found 303.0661.

(E)-3-Benzylidene-4-((ethylsulfonyl)methyl)-4-methyldihydrofuran-2(3H)-one (**3an**). White solid (135 mg, 92% yield), mp = 114.8−115.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (s, 1H), 7.43−7.41 (m, 3H), 7.35−7.34 (m, 2H), 4.64 (d, J = 9.6 Hz, 1H), 4.29 (d, J = 9.7 Hz, 1H), 3.33 (d, J = 14.1 Hz, 1H), 2.99 (d, J = 14.1 Hz, 1H), 2.85 (q, J = 7.4 Hz, 2H), 1.71 (s, 3H), 1.22 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.6, 139.5, 133.7, 133.0, 129.5, 128.9, 128.8, 76.2, 56.1 50.1, 41.5, 24.8, 6.6; IR (KBr) ν_{max} 3695, 3113, 2985, 2760, 1755, 1527, 1480, 1310, 1242, 1137 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{15}H_{18}O_4SNa$ 317.0818; Found 317.0820.

(E)-3-Benzylidene-4-((cyclopropylsulfonyl)methyl)-4-methyldihydrofuran-2(3H)-one (**3ao**). Yellow solid (119 mg, 78% yield), mp = 109.2−110.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.77 (s, 1H), 7.43−7.42 (m, 3H), 7.38−7.36 (m, 2H), 4.66 (d, J = 9.6 Hz, 1H), 4.27 (d, J = 9.6 Hz, 1H), 3.45 (d, J = 14.2 Hz, 1H), 3.15 (d, J = 14.3 Hz, 1H), 1.72 (s, 3H), 1.24−1.23 (m, 1H), 1.12−1.11 (m, 2H), 0.97−0.95 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.7, 139.6 133.4, 132.9, 129.6, 129.1, 128.8, 76.3, 58.4, 41.5, 31.9, 24.7, 5.2, 5.1; IR (KBr) ν_{max} 3694, 3112, 2983, 2766, 1754, 1639, 1526, 1478, 1321, 1246, 1136 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{16}H_{18}O_4SNa$ 329.0818; Found 329.0816.

(E)-4-Methyl-3-(4-methylbenzylidene)-4-((phenylsulfonyl)-methyl)dihydrofuran-2(3H)-one (**3ba**). Yellow solid (137 mg, 77% yield), mp = 140.2−140.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.8 Hz, 2H), 7.65 (s, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.24−7.16 (m, 4H), 4.72 (d, J = 9.6 Hz, 1H), 4.26 (d, J = 9.6 Hz, 1H), 3.63 (d, J = 14.6 Hz, 1H), 3.20 (d, J = 14.6 Hz, 1H), 2.38 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 140.5, 140.1, 139.9, 134.0, 131.3, 130.2, 129.5, 129.4, 129.4, 127.4, 76.3, 60.7, 41.8, 24.2, 21.3; IR (KBr) ν_{max} 3689, 3112, 2983, 2772, 1751, 1637, 1524, 1478, 1310, 1242, 1145 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{20}O_4SNa$ 379.0975; Found 379.0978.

3-(4-Ethylbenzylidene)-4-methyl-4-((phenylsulfonyl)methyl)-dihydrofuran-2(3H)-one (**3ca**). Yellow solid (137 mg, 74% yield), mp = 131.7−132.8 °C, ***E*** **isomer** + ***Z*** **isomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.70 (d, J = 8.0 Hz, 2H), 7.60 (s, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (d, J = 7.4 Hz, 2H), 7.22−7.09 (m, 4H), 4.65 (d, J = 9.6 Hz, 1H), 4.21 (d, J = 9.6 Hz, 1H), 3.55 (d, J = 14.6 Hz, 1H), 3.12 (d, J = 14.6 Hz, 1H), 2.60 (dt, J = 15.2, 7.6 Hz, 2H), 1.64 (s, J = 8.0 Hz, 3H), 1.18 (t, J = 7.3 Hz, 3H); ***E*** **isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.9, 146.4, 140.5, 139.9, 133.9, 131.4, 130.4, 129.6, 129.4, 128.2, 127.4, 76.4, 60.6, 41.8, 28.7, 24.3, 15.2; IR(KBr) ν_{max} 3691, 3112, 2980, 2769, 1752, 1636, 1525, 1478, 1311, 1144 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{21}H_{22}O_4SNa$ 393.1131; Found 393.1133.

3-(4-Fluorobenzylidene)-4-methyl-4-((phenylsulfonyl)methyl)-dihydrofuran-2(3H)-one (**3da**). Yellow solid (75.6 mg, 70% yield), mp = 133.2−134.6 °C; ***E*** **isomer** + ***Z*** **isomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95−7.89 (m, 0.75H), 7.85−7.73 (m, 2H), 7.65 (t, J = 7.3 Hz, 1.6H), 7.55 (dd, J = 13.6, 6.2 Hz, 2H), 7.31 (dd, J = 7.9, 5.6 Hz, 1.4H), 7.12−7.10 (m, 2H), 6.76 (s, 0.25H), 4.74 (d, J = 9.6 Hz, 1H), 4.27 (d, J = 9.6 Hz, 1H), 3.50 (d, J = 14.5 Hz, 1H), 3.19 (d, J = 14.5 Hz, 1H), 3.56−3.13 (m, 2H), 1.69 (s, 3H); ***E*** **isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 163.2 (d, J = 251.7 Hz), 140.4, 138.5, 134.1, 133.4 (d, J = 8.7 Hz), 132.3, 131.4 (d, J = 8.4 Hz), 129.5, 127.4, 116.0 (d, J = 22.0 Hz), 76.3, 60.8, 41.8, 24.3; IR (KBr) ν_{max} 3685, 3114, 2982, 1753, 1639, 1526, 1309, 1143 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{17}FO_4SNa$ 383.0724; Found 383.0726.

3-(4-Chlorobenzylidene)-4-methyl-4-((phenylsulfonyl)methyl)-dihydrofuran-2(3H)-one (**3ea**). Yellow solid (122 mg, 65% yield), mp = 124.6−125.4 °C; ***E*** **isomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.7 Hz, 2H), 7.63 (d, J = 7.5 Hz, 1H), 7.59 (s, 1H), 7.51 (t, J = 7.7

DOI: 10.1021/acs.joc.6b02416
J. Org. Chem. 2017, 82, 1224−1230

Hz, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 4.73 (d, J = 9.6 Hz, 1H), 4.22 (d, J = 9.6 Hz, 1H), 3.44 (d, J = 24.1 Hz, 1H), 3.22 (d, J = 14.6 Hz, 1H), 1.60 (s, 3H); ***E* isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 140.2, 138.2, 135.5, 134.0, 132.8, 131.5, 130.4, 129.4, 128.9, 127.3, 76.0, 60.7, 41.7, 24.4; IR (KBr) ν_{max} 3692, 3100, 2983, 2770, 1752, 1637, 1523, 1485, 1308, 1245, 1148 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{17}ClO_4SNa$ 399.0428; Found 399.0432.

*4-Methyl-4-((phenylsulfonyl)methyl)-3-(4-(trifluoromethyl)-benzylidene)dihydrofuran-2(3H)-one (**3fa**).* Yellow solid (153 mg, 75% yield), mp = 141.5−142.9 °C; ***E* isomer + *Z* isomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.96−7.77 (m, 2H), 7.79−7.69 (m, 2H), 7.62 (t, J = 9.1 Hz, 3H), 7.56−7.48 (m, 3H), 7.40 (d, J = 8.0 Hz, 1H), 4.76 (d, J = 9.6 Hz, 1H), 4.23 (d, J = 9.6 Hz, 1H), 3.32 (d, J = 14.5 Hz, 1H), 3.20 (d, J = 14.5 Hz, 1H), 1.57 (s, 3H); ***E* isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.1, 140.2, 137.7, 137.1, 134.4, 134.1, 130.0 (q, J = 224.0 Hz), 129. 5, 129.1, 127.5, 127.2, 125.5 (q, J = 3.5 Hz), 75.8, 61.1, 41.8, 24.9; ***E* isomer** ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −62.86 (s); IR (KBr) ν_{max} 3692, 3110, 2983, 2771, 1754, 1641, 1526, 1477, 1322, 1141 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{17}F_3O_4SNa$ 433.0692; Found 433.0695.

*(E)-4-Methyl-3-(3-methylbenzylidene)-4-((phenylsulfonyl)-methyl)dihydrofuran-2(3H)-one (**3ga**).* Yellow solid (106 mg, 60% yield), mp = 137.7−138.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.76 (d, J = 7.6 Hz, 2H), 7.69 (s, 1H), 7.64 (t, J = 7.3 Hz, 1H), 7.53 (t, J = 7.5 Hz, 2H), 7.32−7.25 (m, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.11 (s, 2H), 4.71 (d, J = 9.6 Hz, 1H), 4.30 (d, J = 9.6 Hz, 1H), 3.60 (d, J = 14.5 Hz, 1H), 3.18 (d, J = 14.5 Hz, 1H), 2.35 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.8, 140.7, 140.0, 138.6, 134.0, 133.2, 132.3, 130.4, 130.0, 129.5, 128.6, 127.4, 126.2, 76.4, 61.0, 41.9, 24.6, 21.4; IR (KBr) ν_{max} 3690, 3110, 2982, 2770, 1754, 1641, 1525, 1478, 1311, 1146 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{20}O_4SNa$ 379.0975; Found 379.0974.

*(E)-3-(3-Chlorobenzylidene)-4-methyl-4-((phenylsulfonyl)-methyl)dihydrofuran-2(3H)-one (**3ha**).* Yellow oil (112 mg, 60% yield), ***E* isomer + *Z* isomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.82−7.64 (m, 2H), 7.58−7.49 (m, 2H), 7.46−7.43 (m, 2H), 7.28−7.13 (m, 3H), 7.09 (d, J = 5.9 Hz, 0.75H), 6.69 (s, 0.25H), 4.47−4.67 (m, 1H), 4.19−4.08 (m, 1H), 3.41−3.11 (m, 2H), 1.58 (s, 1.25H), 1.48 (s, 1.75H). ***E* isomer + *Z* isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.1, 167.5, 140.4, 140.2, 138.5, 137.8, 134.9, 134.5, 134.2, 134.0, 133.9, 133.6, 133.6, 132.5, 130.4, 129.9, 129.6, 129.5, 129.4, 129.3, 129.2, 128.8, 128.7, 127.4, 127.2, 126.8, 75.8, 74.3, 63.0, 60.9, 43.6, 41.6, 24.8, 24.6. IR (KBr) ν_{max} 3689, 3107, 2981, 2772, 1755, 1641, 1562, 1477, 1309, 1145 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{17}ClO_4SNa$ 399.0428; Found 399.0432.

*3-(3-Bromobenzylidene)-4-methyl-4-((phenylsulfonyl)methyl)-dihydrofuran-2(3H)-one (**3ia**).* Yellow oil (94 mg, 45% yield); ***E* isomer + *Z* isomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.92−7.85 (m, 1.5H), 7.78 (d, J = 7.7 Hz, 1H), 7.66 (dd, J = 23.8, 8.6 Hz, 2H), 7.53 (dd, J = 16.6, 8.5 Hz, 2.5H), 7.47−7.39 (m, 1H), 7.30−7.17 (m, 1.5H), 6.77 (s, 0.0.5H), 4.84−4.76 (m, 1H), 3.50−3.19 (m, 2H), 1.67 (s, 0.5H), 1.57 (s, 0.5H); ***E* isomer + *Z* isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.0, 167.5, 140.4, 140.2, 138.4, 137.7, 135.2, 134.5, 134.0, 133.9, 133.7, 133.3, 132.6, 132.5, 132.2, 131.6, 130.1, 129.6, 129.4, 129.2, 127.5, 127.3, 127.2, 122.5, 121.8 75.8, 74.3, 63.1, 60.9, 43.7, 41.7, 24.8, 24.6; IR (KBr) ν_{max} 3689, 3108, 2981, 2769, 1750, 1636, 1555, 1476, 1306, 1141 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{17}BrO_4SNa$ 442.9923; Found 442.9925.

*3-(2-Fluorobenzylidene)-4-methyl-4-((phenylsulfonyl)methyl)-dihydrofuran-2(3H)-one (**3ja**).* Yellow oil (120 mg, 67%yield); ***E* isomer + *Z* isomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.82−7.64 (m, 2H), 7.65−7.61 (m, 2H), 7.58−7.48 (m, 2H), 7.39 (dd, J = 13.4, 7.1 Hz, 1H), 7.21 (dt, J = 25.7, 7.4 Hz, 2H), 7.09 (t, J = 8.9 Hz, 1H), 4.79 (d, J = 9.5 Hz, 1H), 4.22 (d, J = 9.7 Hz, 1H), 3.43 (d, J = 15.8 Hz, 1H), 3.26 (d, J = 14.4 Hz, 1H), 1.53 (s, 3H); ***E* isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 169.9, 159.5 (d, J = 247.6 Hz), 140.3, 135.0, 133.9, 132.2 (d, J = 2.9 Hz), 131.3 (d, J = 8.2 Hz), 129.9 (d, J = 2.2 Hz), 129.3, 127.2, 124.1 (d, J = 3.6 Hz), 121.0 (d, J = 15.0 Hz), 115.9 (d, J = 21.5 Hz), 75.5, 60.5, 42.0, 23.5; ***Z* isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 167.4, 160.2 (d, J = 253.1 Hz), 140.4, 133.4, 131.7, 131.3, 131.6(d, J = 6.7 Hz), 129.4 (d, J = 11.9 Hz), 127.5, 127.4, 123.4 (d, J = 3.6 Hz), 120.5 (d, J = 12.0 Hz), 114.9 (d, J = 21.9 Hz), 74.3, 63.1, 43.5, 24.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.68, −113.48; IR (KBr) ν_{max} 3688, 3105, 2981, 2769, 1757, 1653, 1568, 1482, 1310, 1146 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{17}FO_4SNa$ 383.0724; Found 383.0728.

*(E)-3-Ethylidene-4-methyl-4-((phenylsulfonyl)methyl)dihydro-furan-2(3H)-one (**3la**).* Yellow solid (91 mg, 65% yield), mp = 136.8−138.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.89 (d, J = 7.4 Hz, 2H), 7.69−7.63 (m, 1H), 7.57 (t, J = 7.6 Hz, 2H), 6.20 (q, J = 7.3 Hz, 1H), 4.72 (d, J = 9.7 Hz, 1H), 4.13 (d, J = 9.8 Hz, 1H), 3.32−3.15 (m, 2H), 2.12 (d, J = 7.3 Hz, 3H), 1.56 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 168.9, 140.7, 139.8, 134.0, 132.6, 129.5, 127.6, 74.6, 63.5, 42.5, 24.7, 13.8; IR (KBr) ν_{max} 3692, 3111, 2982, 2769, 1753, 1662, 1528, 1479, 1310, 1147 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{14}H_{16}O_4SNa$ 303.0662; Found 303.0660.

*(E)-3-Hexylidene-4-methyl-4-((phenylsulfonyl)methyl)dihydro-furan-2(3H)-one (**3ma**).* Yellow solid (104 mg, 62% yield), mp = 84.1−85.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.7 Hz, 2H), 7.67−7.61 (m, 1H), 7.58−7.54 (m, 2H), 6.09 (t, J = 7.6 Hz, 1H), 4.70 (d, J = 9.7 Hz, 1H), 4.12 (d, J = 9.7 Hz, 1H), 3.34−3.14 (m, 2H), 2.78−2.47 (m, 2H), 1.55 (s, 3H), 1.42−1.32 (m, 2H), 1.26−1.25 (m, 2H), 0.84 (t, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 168.7, 145.2, 140.6, 134.0, 131.7, 129.5, 127.5, 74.5, 63.5, 42.3, 31.2, 28.5, 27.2, 24.8, 22.3, 13.8; IR (KBr) ν_{max} 3682, 3110, 2971, 2761, 1751, 1662, 1527, 1477, 1307, 1141 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{18}H_{24}O_4SNa$ 359.1288; Found 359.1289.

*(E)-3-(2,4-Dimethylbenzylidene)-4-methyl-4-((phenylsulfonyl)-methyl)dihydrofuran-2(3H)-one (**3na**).* Yellow solid (120 mg, 72% yield), mp = 136.4−137.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.73 (s, 1H), 7.69 (d, J = 7.7 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.02 (s, 1H), 6.97 (s, 2H), 4.68 (d, J = 9.6 Hz, 1H), 4.25 (d, J = 9.6 Hz, 1H), 3.37 (d, J = 14.5 Hz, 1H), 3.14 (d, J = 14.5 Hz, 1H), 2.32 (s, 3H), 2.18 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.4, 140.5, 139.4, 139.3, 136.5, 133.9, 132.8, 131.2, 129.7, 129.3, 127.9, 127.2, 126.2, 75.8, 61.1, 41.9, 24.9, 21.1, 19.9; IR (KBr) ν_{max} 3687, 3111, 2983, 2771, 1755, 1658, 1527, 1479, 1311, 1147 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{21}H_{22}O_4SNa$ 393.1131; Found 393.1131.

*4-Methyl-4-((phenylsulfonyl)methyl)-3-(thiophen-3-ylmethylene)dihydrofuran-2(3H)-one (**3oa**).* Yellow oil (90 mg, 52% yield); ***E* isomer + *Z* isomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.91−7.82 (m, 2H), 7.66−7.60 (m, 2H), 7.56−7.51 (m, 2H), 7.42 (s, 1H), 7.21 (d, J = 5.0 Hz, 1H), 4.78 (d, J = 9.7 Hz, 1H), 4.29 (d, J = 9.7 Hz, 1H), 3.75 (d, J = 14.6 Hz, 1H), 3.26 (d, J = 14.6 Hz, 1H), 1.81 (s, 2.25H), 1.69 (s, 0.25H); ***E* isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 140.4, 134.1, 133.2, 130.2, 129.6, 129.5, 128.7, 127.6, 127.5, 127.3, 76.9, 60.2, 41.3, 23.3; ***Z* isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 168.3, 140.6, 134.7, 134.1, 134.0, 132.8, 132.4, 130.6, 128.5, 127.6, 125.3, 74.5, 63.6, 43.9, 24.5; IR (KBr) ν_{max} 3692, 3109, 2982, 2769, 1747, 1634, 1528, 1307, 1244, 1141 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{17}H_{16}O_4S_2Na$ 371.0382; Found 371.0385.

*3-Benzylidene-4-ethyl-4-((phenylsulfonyl)methyl)dihydrofuran-2(3H)-one (**3pa**).* Yellow oil (128 mg, 72% yield); ***E* isomer + *Z* isomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.83−7.72 (m, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.42−7.37 (m, 2H), 7.30−7.18 (m, 4H), 4.69 (d, J = 9.9 Hz, 1H), 4.29 (d, J = 10.0 Hz, 1H), 3.41 (d, J = 14.6 Hz, 1H), 3.19 (d, J = 14.5 Hz, 1H), 2.09−1.84 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H); ***E* isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 171.0, 140.8, 140.4, 133.8, 133.3, 130.8, 129.4, 129.3, 128.8, 128.6, 127.2, 73.8, 61.4, 45.5, 31.6, 8.3; ***Z* isomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 167.9, 140.9, 140.5, 133.9, 133.3, 132.6, 129.9, 129.4, 129.1, 127.9, 127.5, 73.2, 62.2, 47.0, 30.8, 7.8; IR (KBr) ν_{max} 3685, 3059, 2976, 2768, 1751, 1639, 1525, 1480, 1308, 1239, 1145 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{20}H_{21}O_4S$ 357.1155; Found 357.1153.

DOI: 10.1021/acs.joc.6b02416
J. Org. Chem. 2017, 82, 1224−1230

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02416.

Spectral data for all new compounds and crystal data for **3aa** (PDF)

Crystallographic data for **3aa** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: cewuwq@scut.edu.cn.

*E-mail: jianghf@scut.edu.cn.

ORCID

Huanfeng Jiang: 0000-0002-4355-0294

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the National Key Research and Development Program of China (2016YFA0602900), the National Natural Science Foundation of China (21472051 and 21490572), and Pearl River S&T Nova Program of Guangzhou (201610010160) for financial support.

■ REFERENCES

(1) For selected articles on improvement of pharmaceutical molecules, see: (a) Gobbi, S.; Zimmer, C.; Belluti, F.; Rampa, A.; Hartmann, R. W.; Recanatini, M.; Bisi, A. *J. Med. Chem.* **2010**, *53*, 5347. (b) Kersten, K. M.; Matzger, A. J. *Chem. Commun.* **2016**, *52*, 5281. (c) Mehta, J. V.; Gajera, S. B.; Patel, M. N. *MedChemComm* **2016**, *7*, 1367. (d) Plano, D.; Karelia, D. N.; Pandey, M. K.; Spallholz, J. E.; Amin, S.; Sharma, A. K. *J. Med. Chem.* **2016**, *59*, 1946. (e) Tan, D.; Loots, L.; Friscic, T. *Chem. Commun.* **2016**, *52*, 7760. (f) Xu, W.; Wang, X.-B.; Wang, Z.-M.; Wu, J.-J.; Li, F.; Wang, J.; Kong, L.-Y. *MedChemComm* **2016**, *7*, 990.

(2) For selected articles on sulfones, see: (a) Tfelt-Hansen, P.; DeVries, P.; Saxena, P. R. *Drugs* **2000**, *60*, 1259. (b) Schellhammer, P. F *Expert Opin. Pharmacother.* **2002**, *3*, 1313. (c) Mitchell, G.; Bartlett, D. W.; Fraser, T. E. M.; Hawkes, T. R.; Holt, D. C.; Townson, J. K. R.; Wichert, A. *Pest Manage. Sci.* **2001**, *57*, 120. (d) Boger, P. *J. Pestic. Sci.* **2003**, *28*, 324. (e) Emmett, E. J.; Hayter, B. R.; Willis, M. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 10204. (f) Richards-Taylor, C. S.; Blakemore, D. C.; Willis, M. C. *Chem. Sci.* **2014**, *5*, 222. (g) Bachi, M. D.; Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Ploypradith, P.; Xie, S.; Shapiro, T. A.; Posner, G. *J. Med. Chem.* **2003**, *46*, 2516. (h) Mitchell, G.; Bartlett, D. W.; Fraser, T. E. M.; Hawkes, T. R.; Holt, D. C.; Townson, J. K.; Wichert, R. A. *Pest Manage. Sci.* **2001**, *57*, 120.

(3) For selected examples for transition-metal-catalyzed reactions, see: (a) Chen, C.; Su, J.; Tong, X. *Chem. - Eur. J.* **2013**, *19*, 5014. (b) Ma, X.-T.; Dai, R.-H.; Zhang, J.; Gu, Y.; Tian, S.-K. *Adv. Synth. Catal.* **2014**, *356*, 2984. (c) Taniguchi, N. *Eur. J. Org, Chem.* **2014**, *2014*, 5691. (d) Taniguchi, T.; Idota, A.; Ishibashi, H. *Org. Biomol. Chem.* **2011**, *9*, 3151. (e) Zeng, X.; Ilies, L.; Nakamura, E. *Org. Lett.* **2012**, *14*, 954.

(4) For selected examples for free-radical-mediated reactions, see: (a) Gao, Y.; Wu, W.; Huang, Y.; Huang, K.; Jiang, H. *Org. Chem. Front.* **2014**, *1*, 361. (b) Meyer, A. U.; Jäger, S.; Hari, D. P.; König, B. *Adv. Synth. Catal.* **2015**, *357*, 2050. (c) Wei, W.; Liu, C.; Yang, D.; Wen, J.; You, J.; Wang, H. *Adv. Synth. Catal.* **2015**, *357*, 987. (d) Xiao, F.; Chen, H.; Xie, H.; Chen, S.; Yang, L.; Deng, G.-J. *Org. Lett.* **2014**, *16*, 50. (e) Zheng, L.; Zhou, Z.-Z.; He, Y.-T.; Li, L.-H.; Ma, J.-W.; Qiu, Y.-F.; Zhou, P.-X.; Liu, X.-Y.; Xu, P.-F.; Liang, Y.-M. *J. Org. Chem.* **2016**, *81*, 66.

(5) For selected examples for α-methylene-γ-butyrolactone products, see: (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94. (b) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426. (c) Hu, J.-F.; Patel, R.; Li, B.; Garo, E.; Hough, G. W.; Goering, M. G.; Yoo, H.-D.; O'Neil-Johnson, M.; Eldridge, G. R. *J. Nat. Prod.* **2007**, *70*, 604. (d) Hwang, D.-R.; Wu, Y.-S.; Chang, C.-W.; Lien, T.-W.; Chen, W.-C.; Tan, U.-K.; Hsu, J. T. A.; Hsieh, H.-P. *Bioorg. Med. Chem.* **2006**, *14*, 83.

(6) (a) Lachia, M.; Wolf, H. C.; De Mesmaeker, A. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2123. (b) Li, R.-J.; Zhu, R.-X.; Zhou, J.-C.; Zhang, J.-Z.; Wang, S.; Ye, J.-P.; Wang, Y.-H.; Morris-Natschke, S. L.; Lee, K.-H.; Lou, H.-X. *J. Nat. Prod.* **2013**, *76*, 1700. (c) Ramachandran, P. V.; Pratihar, D.; Nair, H. N. G.; Walters, M.; Smith, S.; Yip-Schneider, M. T.; Wu, H.; Schmidt, C. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6620. (d) Xu, Y.-J.; Tang, C.-P.; Tan, M.-J.; Ke, C.-Q.; Wu, T.; Ye, Y. *Chem. Biodiversity* **2010**, *7*, 151. (e) Ramachandran, P. V.; Nicponski, D. R.; Nair, H. N. G.; Helppi, M. A.; Gagare, P. D.; Schmidt, C. M.; Yip-Schneider, M. T. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6911.

(7) For selected examples for constructing the lactone skeletons, see: (a) Kitagaki, S.; Shibata, D.; Mukai, C. *Tetrahedron Lett.* **2007**, *48*, 1735. (b) Raju, A. R.; Le, T.; Taylor, C. D.; Howell, A. R. *Org. Lett.* **2007**, *9*, 1699. (c) Yin, G.; Liu, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5442. (d) Tong, X.; Li, D.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 7601. (e) Edwards, M. G.; Kenworthy, M. N.; Kitson, R. R. A.; Scott, M. S.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 1935.

(8) (a) Jang, H.-Y.; Gong, H.; Zhang, J.; Brodbelt, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 6174. (b) Ramachandran, P. V.; Garner, G.; Pratihar, D. *Org. Lett.* **2007**, *9*, 4753. (c) Cateni, F.; Zilic, J.; Zacchigna, M.; Bonivento, P.; Frausin, F.; Scarcia, V. *Eur. J. Med. Chem.* **2006**, *41*, 192. (d) Leclercq, C.; Marko, I. E. *Tetrahedron Lett.* **2005**, *46*, 7229. (e) Hodgson, D. M.; Talbot, E. P. A.; Clark, P. *Org. Lett.* **2011**, *13*, 2594. (f) Yan, Y.; En, D.; Zhuang, Z.; Guo, Y.; Liao, W.-W. *Tetrahedron Lett.* **2014**, *55*, 479.

(9) (a) Zhang, Z.; Wu, W.; Liao, J.; Li, J.; Jiang, H. *Chem. - Eur. J.* **2015**, *21*, 6708. (b) Zhang, Z.; Ouyang, L.; Wu, W.; Li, J.; Zhang, Z.; Jiang, H. *J. Org. Chem.* **2014**, *79*, 10734. (c) Li, J.; Yang, W.; Yang, S.; Huang, L.; Wu, W.; Sun, Y.; Jiang, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 7219. (d) Huang, L.; Wang, Q.; Wu, W.; Jiang, H. *J. Org. Chem.* **2014**, *79*, 7734.

(10) (a) Tang, X.; Huang, L.; Qi, C.; Wu, X.; Wu, W.; Jiang, H. *Chem. Commun.* **2013**, *49*, 6102. (b) Xu, Y.; Tang, X.; Hu, W.; Wu, W.; Jiang, H. *Green Chem.* **2014**, *16*, 3720. (c) Li, X.; Xu, Y.; Wu, W.; Jiang, C.; Qi, C.; Jiang, H. *Chem. - Eur. J.* **2014**, *20*, 7911. (d) Tang, X.; Huang, L.; Xu, Y.; Yang, J.; Wu, W.; Jiang, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 4205. (e) Xu, Y.; Zhao, J.; Tang, X.; Wu, W.; Jiang, H. *Adv. Synth. Catal.* **2014**, *356*, 2029.

(11) For examples using the sodium sulfinates as the sulfonyl sources, see: (a) Chen, C.; Waser, J. *Org. Lett.* **2015**, *17*, 736. (b) Emmett, E. J.; Hayter, B. R.; Willis, M. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 10204. (c) Xiao, F.; Chen, H.; Xie, H.; Chen, S.; Yang, L.; Deng, G.-J. *Org. Lett.* **2014**, *16*, 50.

(12) CCDC 1483589 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) Li, Y.-M.; Sun, M.; Wang, H.-L.; Tian, Q.-P.; Yang, S.-D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3972.

(14) Li, Z.; Zhang, Y.; Zhang, L.; Liu, Z.-Q. *Org. Lett.* **2014**, *16*, 382.

(15) Wu, W.; Yi, S.; Jiang, H. *Chin. Pat. Appl.* 105481806, April 13, 2016.

DOI: 10.1021/acs.joc.6b02416
J. Org. Chem. 2017, 82, 1224−1230