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Stereocontrolled Synthesis of Sulfonyl 2,5-Diaryltetrahydrofurans

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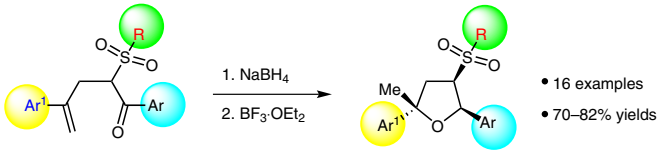

Ar = Ph, 4-FC_6H_4, Tol, 4-$O_2NC_6H_4$, 4-$F_3CC_6H_4$, 4-PhC_6H_4, 2-naphthyl
Ar^1 = Ph, 4-FC_6H_4, 4-PhC_6H_4
R = Tol, Ph

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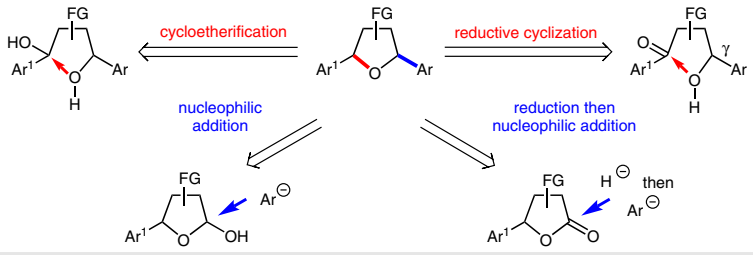
Abstract BF_3·OEt_2-mediated stereocontrolled annulation of 4-alkenols affords sulfonyl 2,5-diaryltetrahydrofurans in good yields. The key synthetic route combines the facile stereoselective reduction of α-styryl-β-ketosulfones and an intramolecular Friedel–Crafts electrophilic cyclization of the resulting 4-alkenols. A plausible mechanism has been studied and proposed.

Key words 2,5-diaryltetrahydrofurans, reduction, 4-alkenols, β-ketosulfones, cyclization

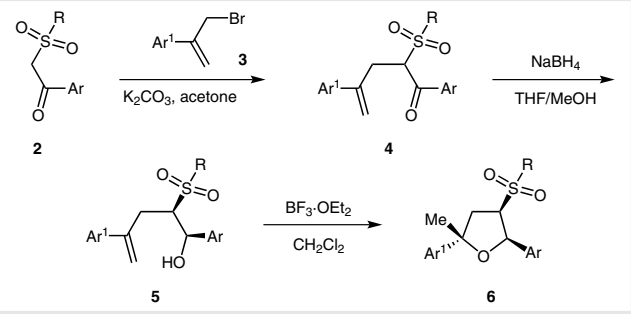
The tetrahydrofuran moiety is an important component in numerous diversified molecules with biological activities of synthetic intermediates and natural products.[1] Among these building blocks, substituted 2,5-diaryltetrahydrofuran can be widely found from natural sources and bioactive molecules including manassantins A and B,[2a,b] virgatusin,[2c–f] talaumidin[2g] and MK-287.[2h,i] As a result, numerous synthetic approaches have been developed for the construction of diversified 2,5-diaryltetrahydrofurans.[2] For various protocols on the synthesis of 2,5-diaryltetrahydrofurans **1**, intramolecular cycloetherification of 1,4-butandiols and reductive cyclization of γ-hydroxyketones are common pathways. Synthetic routes to organometal (Mg, Cu or Zn)-mediated nucleophilic addition of cyclic hemiacetals or lactones have been documented (see Scheme 1).

However, the reported preparation of these derivatives often presents drawbacks (e.g. multistep operations and harsh conditions, poorer stereoselectivity), and this has encouraged organic researchers to explore more efficient synthetic protocols. To the best of our knowledge, for the synthesis of sulfonyl 2,5-diaryltetrahydrofurans, no examples of the intramolecular electrophilic annulation of 4-alkenols have been reported.

In continuation of our investigation into the synthetic applications of β-ketosulfones,[3] a three-step stereoselective synthetic route to sulfonyl 2,5-diaryltetrahydrofurans **6** has been developed, including (i) a K_2CO_3-mediated α-allylation of β-ketosulfones **2** with styryl bromide **3** (prepared from allylic bromination of α-methylstyrene with NBS in refluxing $CHCl_3$) in boiling acetone, (ii) a $NaBH_4$-mediated stereoselective reduction of α-styryl-β-ketosulfones **4** in cooling co-solvent of THF and MeOH (1:1) and (iii) an intramolecular BF_3·OEt_2-mediated stereocontrolled Friedel–Crafts an-



Scheme 1 Synthetic routes of 2,5-diaryltetrahydrofurans



Scheme 2 Our synthetic route to **6**

nulation of the resulting sulfonyl 4-alkenols **5** in CH_2Cl_2 at 25 °C (see Scheme 2).

After further comparison of literature and our previous studies on the Lewis acid triggered annulation,[3,4] substrate **4a** was first examined. α-Styryl-β-ketosulfone **4a** (Ar = Ar^1 = Ph; R = Tol) was chosen as the model's starting material[3f] to examine $NaBH_4$-mediated stereoselective reduction. Under the above conditions, **5a** was isolated in a 90% yield. According to the Felkin–Anh model,[5] the steric hindrance of sulfonyl substituent should inhibit the carbonyl addition of hydride such that the hydride should attack the carbonyl face with the face with less repulsion to form sulfonyl 4-alkenols **5a** via a possible intermediate **A**. Next, intramolecular annulation of **5a** with BF_3·OEt_2 provided **6a** in a 90% yield. The possible mechanism should be initiated to form **B1** or **B2** by complexation of a hydroxyl motif of **5a** with BF_3·OEt_2 via a chair conformation (Scheme 3). **B1** should form the preferred orientation with a *syn*-protonation due to **B2** providing more repulsion between the phenyl group and the OBF_3 complex. Proton exchange of **B1** affords a tertiary carbocation **C**, which, following an intramolecular addition and loss of BF_3, is able to provide **6a** (72%). The structure and relative stereochemistry of **6a** were determined from ^{1}H NMR and *J* coupling analysis. In the ^{1}H NMR spectrum, the equatorial proton (blue symbol) of C-2 shows a doublet with a coupling constant *J* = 8.0 Hz at δ = 5.12 ppm, which indicates that the proton (black symbol) of C-3 is coupling with an axial position [δ = 3.99 (q, *J* = 8.0 Hz)]. The structural frameworks of **6a** (Figure 1) and **6b** (Figure 2) with *trans*-diphenyl substituents were determined by single-crystal X-ray crystallography.[6]

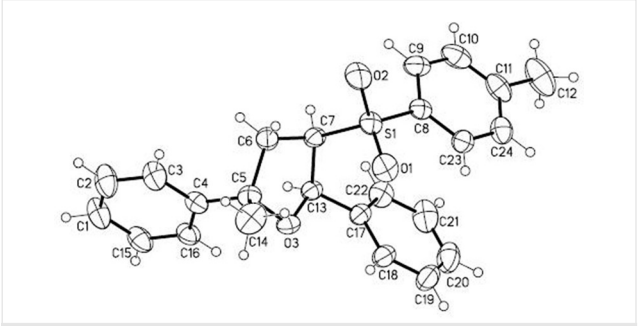


Figure 1 X-ray crystal structure of **6a**

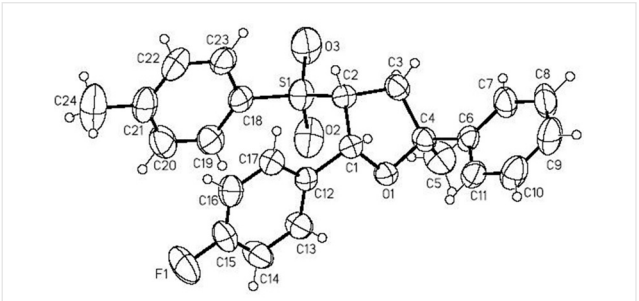
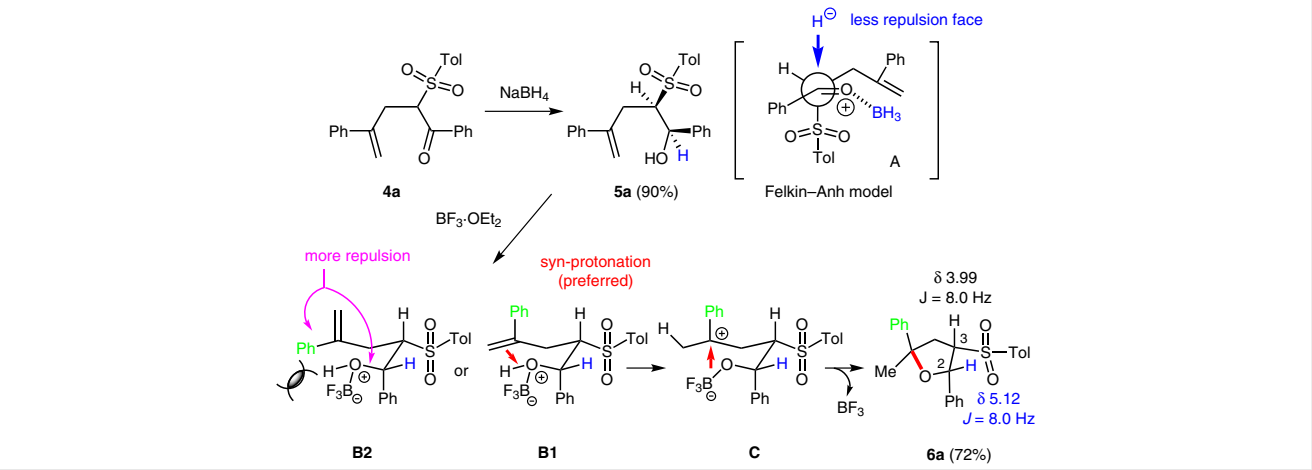


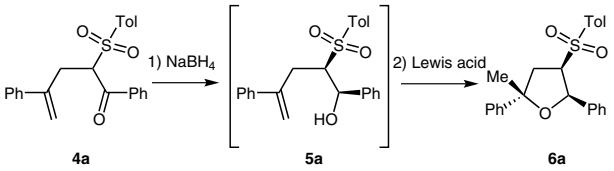
Figure 2 X-ray crystal structure of **6b**



Scheme 3 Possible mechanism

However, **5a** was converted slowly into **6a** at 25 °C in the presence of a $CDCl_3$ solution. It is also very likely that the trace acid in $CDCl_3$ catalyzed the intramolecular annulation. To prevent this unexpected result, **5a** was immediately reacted with $BF_3{\cdot}OEt_2$. With these results in hand, the one-pot conversion from **4a** into **6a** was examined next (Table 1).

Table 1 One-Pot Conditions[a]



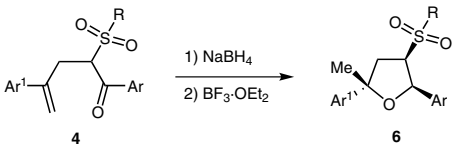
4a **5a** **6a**

Entry	Lewis acid (equiv), solvent, temp (°C)	6[a] (%)[b]
1	$BF_3{\cdot}OEt_2$ (1.0), CH_2Cl_2, 25	75
2	$BF_3{\cdot}OEt_2$ (2.0), CH_2Cl_2, 25	70
3	$BF_3{\cdot}OEt_2$ (0.5), CH_2Cl_2, 25	48[c] (58)[d]
4	$BF_3{\cdot}OEt_2$ (1.0), $(CH_2Cl)_2$, 25	69
5	$BF_3{\cdot}OEt_2$ (1.0), $(CH_2Cl)_2$, 84	40[e] (26)[f]
6	*p*-TsOH (1.0), CH_2Cl_2, 25	63[g]
7	PPA (1.0), CH_2Cl_2, 25	–[h]

[a] Reaction conditions: (1) **4a** (1.0 mmol), $NaBH_4$ (3 equiv), MeOH–THF (1:1; 10 mL), 0 °C, 1 h. (2) Resulting crude **5a**, solvent (5 mL), 25 °C, 20 h.
[b] Isolated yields.
[c] Compound **5a** was recovered (13%).
[d] Reaction time was 40 h and trace amounts of **5a** were recovered.
[e] A complex mixture was isolated in 32% yield.
[f] Reaction time was 40 h and 43% of complex mixture was isolated.
[g] Compound **5a** was recovered (10%).
[h] Unknown products were observed.

Following the sequential reduction–hydroalkoxylation, **6a** was isolated in a 75% yield over two steps via a one-pot $NaBH_4$ (3 equiv)-mediated reduction followed by treatment of the resulting **5a** with $BF_3{\cdot}OEt_2$ (1.0 equiv). Compared with the yield (65%) of the two divided steps, the one-pot reaction condition could increase the efficiency of the overall yields of **6a** (Table 1, entry 1). Furthermore, the amounts (2.0 or 0.5 equiv) of $BF_3{\cdot}OEt_2$, reaction solvents [CH_2Cl_2 or $(CH_2Cl)_2$] and temperatures (25 °C or 84 °C) were also examined. However, attempts to provide a higher yield of **6a** were unsuccessful. In entry 2 (Table 1), no obvious yield changes were observed when 2.0 equivalents of $BF_3{\cdot}OEt_2$ were used. To decrease the amount of $BF_3{\cdot}OEt_2$ (0.5 equiv), **6a** was isolated in a 48% yield along with the recovery of **5a** (13%), as shown in entry 3 (Table 1). With a long reaction time (40 h), a similar yield distribution was observed. Changing the reaction solvent from CH_2Cl_2 to $(CH_2Cl)_2$, **6a** was produced in a 69% yield (see entry 4 in Table 1). After elevating the temperature (r.t. → reflux), the desired **6a** was only isolated in a 40% yield (see entry 5 in Table 1). When the reaction time was prolonged, a complex mixture was isolated in a higher (43%) yield in boiling $(CH_2Cl)_2$ after 40 hours. As shown in entries 6 and 7 (Table 1), Brønsted acids, such as *p*-TsOH and polyphosphoric acid (PPA), showed different catalytic activities. *p*-TsOH provided a similar result with entry 4 (Table 1), but PPA provided unknown products. On the basis of a higher yield and activity, we believe that 1.0 equivalent of $BF_3{\cdot}OEt_2$ should be the optimal reagent (Table 1, entry 1) after examining the formation of skeleton **6**. With the one-pot reaction conditions in hand (Table 1, entry 1, **4a** → **6a**), we further explored the scope for the conversion of other substrates, and the results are shown in Table 2. For the Ar, Ar^1 and R groups of **4a**–**p**, the aryl rings (Ar = Ph, 4-FC_6H_4, Tol, 4-$NO_2C_6H_4$, 4-$CF_3C_6H_4$, 4-PhC_6H_4, Naph; Ar^1 = Ph, 4-FC_6H_4, 4-PhC_6H_4; R = Tol, Ph), with electron-neutral or electron-donating groups were well tolerated, providing the desired **6a**–**p** in moderate to good yields (70–82%).[7]

Table 2 Synthesis of **6**[a]



4 **6**

Entry	**4**, Ar, Ar^1, R	**6**, Yield (%)[b]
1	**4a**, Ph, Ph, Tol	**6a**, 75
2	**4b**, 4-FC_6H_4, Ph, Tol	**6b**, 70
3	**4c**, 4-MeC_6H_4, Ph, Tol	**6c**, 70
4	**4d**, 4-$O_2NC_6H_4$, Ph, Tol	**6d**, 80
5	**4e**, 4-$F_3CC_6H_4$, Ph, Tol	**6e**, 82
6	**4f**, 4-PhC_6H_4, Ph, Tol	**6f**, 73
7	**4g**, Naph, Ph, Tol	**6g**, 76
8	**4h**, Naph, 4-FC_6H_4, Tol	**6h**, 75
9	**4i**, Naph, 4-PhC_6H_4, Tol	**6i**, 70
10	**4j**, Ph, 4-PhC_6H_4, Tol	**6j**, 73
11	**4k**, Tol, 4-PhC_6H_4, Tol	**6k**, 70
12	**4l**, 4-PhC_6H_4, 4-PhC_6H_4, Tol	**6l**, 76
13	**4m**, Ph, Ph, Ph	**6m**, 70
14	**4n**, 4-FC_6H_4, Ph, Ph	**6n**, 78
15	**4o**, 4-PhC_6H_4, Ph, Ph	**6o**, 75
16	**4p**, 4-PhC_6H_4, 4-PhC_6H_4, Ph	**6p**, 74

[a] Reaction conditions: (1) **4** (1.0 mmol), $NaBH_4$ (3.0 equiv), MeOH (5 mL), THF (5 mL), 0 °C, 1 h (2) $BF_3{\cdot}OEt_2$ (1.0 equiv), CH_2Cl_2 (5 mL), 25 °C, 20 h.
[b] Isolated yield.

In summary, we have developed a mild, facile and one-pot synthesis of 2,5-diaryltetrahydrofurans **6** in good yields via a $NaBH_4$-mediated stereocontrolled reduction of α-styryl-β-ketosulfones **4** and an intramolecular $BF_3{\cdot}OEt_2$-mediated Friedel–Crafts electrophilic cyclization of the resulting 4-alkenols **5** under a reduction–hydroalkoxylation process. A plausible mechanism has been discussed and proposed.

Further investigation regarding the synthetic applications of β-ketosulfones will be conducted and published in due course.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560423.

References and Notes

(1) For reviews on the synthesis of tetrahydrofurans, see: (a) Rjabovs, V.; Turks, M. *Tetrahedron* **2013**, *69*, 10693. (b) Bellur, E.; Feist, H.; Langer, P. *Tetrahedron* **2007**, *63*, 10865. (c) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Alvarez, M. *Chem. Rev.* **2013**, *113*, 4567. (d) Jalce, G.; Franck, X.; Figadere, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2537. (e) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261.

(2) For representative examples of 2,5-diaryltetrahydrofuran skeleton in natural products, e.g. manassantin A and B, see: (a) Hanessian, S.; Reddy, G. J.; Chahal, N. *Org. Lett.* **2006**, *8*, 5477. (b) Kim, H.; Kasper, A. C.; Moon, E. J.; Park, Y.; Wooten, C. M.; Dewhirst, M. W.; Hong, J. *Org. Lett.* **2009**, *11*, 89. For virgatusin, see: (c) Akindele, T.; Marsden, S. P.; Cumming, J. G. *Org. Lett.* **2005**, *17*, 3685. (d) Kim, H.; Wooten, C. M.; Park, Y.; Hong, J. *Org. Lett.* **2007**, *9*, 3965. (e) Jahn, U.; Rudakov, D. *Org. Lett.* **2006**, *8*, 4481. (f) Martinet, S.; Meou, A.; Brun, P. *Eur. J. Org. Chem.* **2009**, 2306. For talaumidin, see: (g) Harada, K.; Kubo, M.; Horiuchi, H.; Ishii, A.; Esumi, T.; Hioki, H.; Fukuyama, Y. *J. Org. Chem.* **2015**, *80*, 7076. For MK-287, see: (h) Girotra, N. N.; Ponpipom, M. M.; Acton, J. J.; Alberts, A. W.; Bach, T. N.; Ball, R. G.; Bugianesi, R. L.; Parsons, W. H. *J. Med. Chem.* **1992**, *35*, 3474. (i) Thompson, A. S.; Tschaen, D. M.; Simpson, P.; McSwine, D. J.; Reamer, R. A.; Verhoeven, T. R.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 7044. During the preparation of this manuscript, Saikia and co-workers demonstrated the feasibility of this BF_3·OEt_2-mediated annulations, see: (j) Sultana, S.; Devi, N. R.; Saikia, A. K. *Asian J. Org. Chem.* **2015**, *4*, 1281. (k) Ghosh, P.; Deka, M. J.; Saikia, A. K. *Tetrahedron* **2016**, *72*, 690.

(3) (a) Chang, M.-Y.; Chen, Y.-C.; Chan, C.-K. *Tetrahedron* **2014**, *70*, 8908. (b) Chang, M.-Y.; Cheng, Y.-J.; Lu, Y.-J. *Org. Lett.* **2014**, *16*, 6252. (c) Chang, M.-Y.; Lu, Y.-J.; Cheng, Y.-C. *Tetrahedron* **2015**, *71*, 1192. (d) Chang, M.-Y.; Cheng, Y.-J.; Lu, Y.-J. *Org. Lett.* **2015**, *17*, 1264. (e) Chang, M.-Y.; Cheng, Y.-J.; Lu, Y.-J. *Org. Lett.* **2015**, *17*, 3142. (f) Chang, M.-Y.; Cheng, Y.-J. *Org. Lett.* **2015**, *17*, 5702.

(4) For recent syntheses of β-ketosulfones, see: (a) Pospisil, J.; Sato, H. *J. Org. Chem.* **2011**, *76*, 2269. (b) Sreedhar, B.; Rawat, V. S. *Synlett* **2012**, *23*, 413. (c) Kumar, A.; Muthyala, M. K. *Tetrahedron Lett.* **2011**, *52*, 5368. (d) Lu, Q.; Zhang, J.; Zhao, G.; Qi, Y.; Wang, H.; Lei, W. *J. Am. Chem. Soc.* **2013**, *135*, 11481. (e) Tsui, G. C.; Glenadel, Q.; Lau, C.; Lautens, M. *Org. Lett.* **2011**, *13*, 208. (f) Zhou, G.; Ting, P. T.; Aslanian, R. G. *Tetrahedron Lett.* **2010**, *51*, 939. (g) Tang, X.; Huang, L.; Xu, Y.; Yang, J.; Wu, W.; Jiang, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 4205. (h) Chawla, R.; Singh, A. K.; Yadav, L. D. S. *Eur. J. Org. Chem.* **2014**, *10*, 2032. (i) Singh, A. K.; Chawla, R.; Yadav, L. D. S. *Tetrahedron Lett.* **2014**, *55*, 4742. (j) Shi, X.; Ren, X.; Ren, Z.; Li, J.; Wang, Y.; Yang, S.; Gu, J.; Gao, Q.; Huang, G. *Eur. J. Org. Chem.* **2014**, *10*, 5083. (k) Xuan, J.; Feng, Z.-J.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *Chem. Eur. J.* **2014**, *20*, 3045.

(5) (a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191. (b) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263. (c) Ager, D. J.; East, M. B. *Tetrahedron* **1992**, *48*, 2803.

(6) CCDC 1429280 (**6a**) and 1434699 (**6b**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

(7) **Representative Synthetic Procedure of Skeleton 6**: $NaBH_4$ (100 mg, 3.0 mmol) was added to a solution of skeleton **4** (1.0 mmol) in a co-solvent of THF (5 mL) and MeOH (5 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and the solvent was concentrated. The residue was diluted with H_2O (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product. Without further purification, BF_3·OEt_2 (142 mg, 1.0 mmol) was added to a solution of the resulting skeleton **5** in CH_2Cl_2 (5 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 20 h. The reaction mixture was concentrated and the residue was diluted with H_2O (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product under reduced pressure. Purification on silica gel (hexanes–EtOAc, 8:1 to 3:1) yielded the skeleton **6**. Compound **6a**: yield: 75% (294 mg); colorless solid; mp 173–174 °C (recrystallized from hexanes and EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.42 (m, 4 H), 7.16–7.30 (m, 8 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 5.12 (d, *J* = 8.0 Hz, 1 H), 3.99 (q, *J* = 8.0 Hz, 1 H), 2.88 (dd, *J* = 1.2, 8.4 Hz, 2 H), 2.37 (s, 3 H), 1.78 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.27, 143.82, 136.26, 135.70, 129.36 (2 ×), 128.62 (2 ×), 128.50 (2 ×), 128.14, 127.82 (2 ×), 127.58 (2 ×), 127.18, 124.50 (2 ×), 83.80, 79.46, 67.64, 40.14, 30.31, 21.48. HRMS (ESI): *m*/*z* [M$^+$ + 1] calcd for $C_{24}H_{25}O_3S$: 393.1524; found: 393.1530. Anal. Calcd for $C_{24}H_{24}O_3S$: C, 73.44; H, 6.16. Found: C, 73.70; H, 6.28. Single-crystal X-ray diagram: crystal of compound **6a** was grown by slow diffusion of EtOAc into a solution of compound **6a** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 21/c, *a* = 13.9520(8) Å, *b* = 14.5100(7) Å, *c* = 11.1921(6) Å, *V* = 2096.6(2) Å^3, *Z* = 4, d_{calcd} = 1.243 mg/cm^3, *F*(000) = 832, 2θ range 1.577–26.410°, *R* indices (all data) *R*1 = 0.0729, *wR*2 = 0.1568. Compound **6b**: yield: 70% (287 mg); colorless solid; mp 154–155 °C (recrystallized from hexanes and EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.53 (m, 2 H), 7.37–7.42 (m, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.27–7.29 (m, 3 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 6.89–6.94 (m, 2 H), 5.49 (d, *J* = 8.0 Hz, 1 H), 4.39 (q, *J* = 8.0 Hz, 1 H), 2.85 (dd, *J* = 10.0, 12.8 Hz, 1 H), 2.56 (dd, *J* = 8.4, 12.8 Hz, 1 H), 2.39 (s, 3 H), 1.57 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.55 (d, *J* = 244.8 Hz), 146.02, 144.22, 136.30, 134.10 (d, *J* = 3.0 Hz), 130.26 (d, *J* = 8.4 Hz, 2 ×), 129.45 (2 ×), 128.24 (2 ×), 127.77 (2 ×), 127.00, 124.48 (2 ×), 114.32 (d, *J* = 22.0. Hz, 2 ×), 83.24, 78.72,

67.46, 40.53, 27.80, 21.41. HRMS (ESI): m/z [M^+ + 1] calcd for $C_{24}H_{24}FO_3S$: 411.1430; found: 411.1435. Single-crystal X-ray diagram: crystal of compound **6b** was grown by slow diffusion of EtOAc into a solution of compound **6b** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 21/c, a = 5.8096(3) Å, b = 15.7969(8) Å, c = 22.8181(12) Å, V = 2093.57(19) Å^3, Z = 4, d_{calcd} = 1.302 mg/cm^3, $F(000)$ = 864, 2θ range 1.568–26.542°, R indices (all data) $R1$ = 0.0645, $wR2$ = 0.1086.