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Asymmetric Synthesis of β-Hydroxy Sulfides Controlled by Remote Sulfoxides

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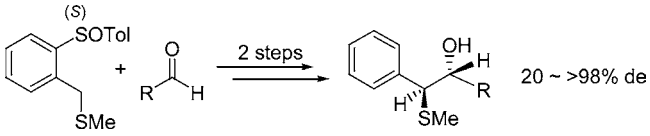

Reactions of (*S*)-α-(methylthio)-2-(*p*-tolylsulfinyl)benzyl carbanion with different carbonyl compounds proceeds with complete control of the configuration at the benzylic position. Aldehydes yield easily separable mixtures of β-hydroxy sulfides, epimers at the hydroxylic carbon, where the stereoselectivity depends on steric factors (from 20% to >98% de).

Enantiopure β-hydroxy sulfides are outstanding structural subunits because of their occurrence in natural products[1] and their importance as valuable intermediates in the synthesis of naturally occurring spiroketal pheromones,[2] chiral oxiranes,[3] thiiranes,[4] tetrahydrofurans,[5] and 4-acetoxyazetidinones.[6] Moreover, they are easily oxidized to β-hydroxy sulfoxides[7] or sulfones,[8] which serve as extremely useful chiral building blocks.

The available synthetic approaches for obtaining enantiopure β-hydroxy sulfides involve both biological and chemical methods. Among the first, the asymmetric reduction of β-keto sulfides using baker's yeast[1a,9] and lipase-mediated kinetic resolution of racemic β-hydroxy sulfides[6,10] have been reported. Chemical methods provide better results, but to our knowledge, only two reactions have been reported. The CBS-oxazaborolidine-catalyzed asymmetric borane reduction of β-ketosulfides[11] affords very high optical and chemical yields, but it has never been applied to α-substituted carbonyl derivatives, thus restricting its scope to the synthesis of hydroxy sulfides only containing one chiral center. The second reaction consists in desymmetrization of cyclic *meso*-epoxides by opening with thiolates assisted by chiral catalysts.[12] The most direct retrosynthetic route to these compounds implies the C(1)−C(2) bond disconnection. So the search for highly stereoselective methods involving nucleophilic addition of prochiral α-thio carbanions to carbonyl compounds would be an efficient and unprecedented path to chiral β-hydroxy sulfides, simultaneously creating two contiguous stereogenic centers in a single step and avoiding the regioselectivity problems in the epoxide opening.

We have recently reported the almost completely stereoselective transference of chiral benzyl groups to different electrophiles[13] mediated by an *o*-sulfinyl group. In particular, the reactions of α-(methylthio)-2-(*p*-tolylsulfinyl)benzyl carbanions with *N*-(*p*-tolylsulfinyl)aldimines evolve in a completely stereoselective manner, providing enantiomerically pure 1,2-amino sulfide derivatives.[14] Bearing in mind these antecedents, we reasoned that the reactions of carbonyl compounds with the α-(methylthio)-2-(*p*-tolylsulfinyl)benzyl carbanion derived from (*S*)-**2** (Scheme 1) could provide a new and easy access to chiral 1,2-diaryl- and 1-alkyl-2-aryl-2-(methylthio)ethanols in a short number of steps. The results obtained in this study are reported in this paper.

The synthesis of (*S*)-α-(methylthio)-2-(*p*-tolylsulfinyl)toluene [(S)-**2**] was performed starting from enantiopure (S)-2-(*p*-tolylsulfinyl)toluene [(S)-**1**] according to the procedure previously reported by us[14a] (Scheme 1). (*S*)-**2** was reacted with LDA (which provides the α-thiocarbanion Li-(*S*)-**2**) followed by further addition of *tert*-butyl chloroformate (**3**). After a detailed

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(1) De Paolis, M.; Blankenstein, J.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2002**, *4*, 1235−1238.
(2) Liu, H.; Cohen, T. *J. Org. Chem.* **1995**, *60*, 2022.
(3) (a) Fujisawa, T.; Itoh, T.; Nakai, M.; Sato, T. *Tetrahedron Lett.* **1985**, *26*, 771−774. (b) Goergens, U.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1064. (c) Sánchez-Obregón, R.; Ortiz, B.; Walls, F.; Yuste, F.; García-Ruano, J. L. *Tetrahedron: Asymmetry* **1999**, *10*, 947.
(4) Dinunno, L.; Franchini, C.; Nacci, A.; Scilimati, A.; Sinicropi, M. S. *Tetrahedron: Asymmetry* **1999**, *10*, 1913.
(5) (a) Gruttadauria, M.; Meo, P.; Noto, R. *Tetrahedron* **1999**, *55*, 1409. (b) Gruttadauria, M.; Meo, P.; Noto, R. *Tetrahedron* **1999**, *55*, 4769.
(6) Nakatsuka, T.; Iwata, H.; Tanaka, R.; Imajo, S.; Ishiguro, M. *J. Chem. Soc., Chem. Commun.* **1991**, 662.
(7) (a) García-Ruano, J. L.; Fernández, M. A.; Maestro, M. C.; Rodríguez, M. M. *Tetrahedron* **2006**, *62*, 1245−1252. (b) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760. (c) Walker, A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 961−998.
(8) Bernabeu, M. C.; Bonete, P.; Caturla, F.; Chinchilla, R.; Nájera, C. *Tetrahedron: Asymmetry* **1996**, *7*, 2475−2478 and references therein.
(9) Fujisawa, T.; Itoh, T.; Yonekawa, Y.; Sato, T. *Tetrahedron Lett.* **1986**, *27*, 5405−5408. (b) Fujisawa, T.; Itoh, T.; Sato, T. *Tetrahedron Lett.* **1984**, *25*, 5083−5086.
(10) (a) Chimni, S. S.; Singh, S.; Kumar, S.; Mahajan, S. *Tetrahedron: Asymmetry* **2002**, *13*, 511−517. (b) Chimni, S. S.; Singh, S.; Kumar, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2457−2462.
(11) Cho, B. T.; Shin, S. H. *Tetrahedron* ***2005***, *61*, *6959*−6966; Cho, B.T.; Choi, O. K.; Kim, D. J. *Tetrahedron: Asymmetry* **2002**, *13*, 697−703.
(12) (a) Yamashita, H.; Mukaiyama, T. *Chem. Lett*. **1985**, 1643−1646. (b) Yamashita, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1213−1220. (c) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783−4784. (d) Wu, M. H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 5252−5254.
(13) (a) García-Ruano, J. L.; Carreño, M. C.; Toledo, M. A.; Aguirre, J. M.; Aranda, M. T.; Fischer, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2736−2737. (b) García-Ruano, J. L.; Alemán, J.; Soriano, J. F. *Org. Lett.* **2003**, *5*, 677−680. (c) García-Ruano, J. L.; Alemán, J. *Org. Lett.* **2003**, *5*, 4513−4516. (d) García-Ruano, J. L.; Aranda, M. T.; Aguirre, J. M. *Tetrahedron* **2004**, *60*, 5383−5392. (e) García-Ruano, J. L.; Alemán, J.; Parra, A. *J. Am. Chem. Soc.* **2005**, *127*, 13048−13054. (f) García-Ruano, J. L.; Aleman, J.; Cid, B. *Synthesis*, **2006**, 687−691.
(14) (a) Arroyo, Y.; Meana, A.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; García-Ruano, J. L. *J. Org. Chem.* **2005**, *70*, 3914−3920. (b) Arroyo, Y.; Meana, A.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; García-Ruano, J. L. *Tetrahedron* **2006**, *62*, 8525−8532.

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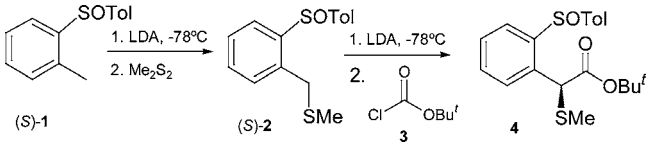
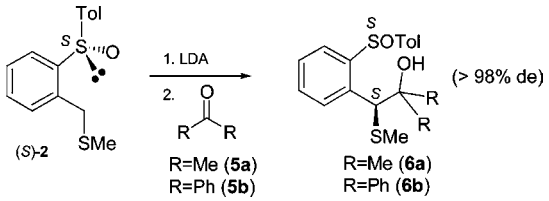
SCHEME 1



SCHEME 2



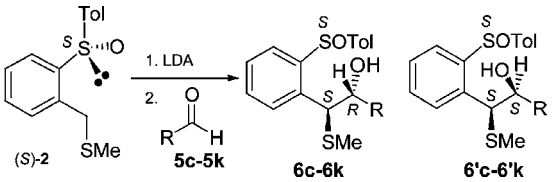
study of the conditions we were able to obtain compound **4** in 89% yield as only one diastereoisomer (>98% de, Scheme 1).[15] These results are obtained through a careful control of the reaction time. The reaction must be stopped after 1 min because longer reaction times determine the formation of mixtures of epimers at benzylic carbon, presumably due to the low configurational stability of the α-lithiobenzyl sulfides.[16]

We then studied the reactions of (*S*)-**2** with the symmetrical ketones **5a** and **5b** (Scheme 2). As in the previous case, the observed stereoselectivity is strongly dependent on the reaction conditions. Under the optimal conditions[15] the reactions are completely stereoselective, only yielding one *β*-hydroxy sulfide (**6a** or **6b**)[17] in higher than 98% de by ^{1}H NMR. We assign the configuration (2*S*,S*S*) to compounds **6a** and **6b** (as well as to **4**) by assuming that the stereochemical course of these reactions is identical to that of the reactions of (*S*)-**2** with *N*-sulfinylimines[14] and other *o*-sulfinylbenzyl carbanions with different electrophiles.[13]

Then we studied the reactions of (*S*)-**2** with aromatic (**5c**−**h**) and aliphatic (**5i**−**k**) aldehydes (Table 1). Benzaldehyde (**5c**) afforded a 75:25 mixture of two alcohols, *anti*-**6c** and *syn*-**6′c**, with the first one being the major one. Similar results were obtained with aldehydes **5d**−**f** of similar size but different electronic density, which indicates the minor influence of this factor on the stereoselectivity. The *anti*:*syn* ratio increased to 84:16 for the aldehyde **5g** (Table 1, entry 5), and only one diastereoisomeric *β*-hydroxy sulfide, **6h** (>98% de), was obtained from **5h** (Table 1, entry 6). This suggests that the stereoselectivity increases when the size of the aldehyde becomes larger. The behavior of the alkyl aldehydes is similar. Valeraldehyde (**5i**) and isobutyraldehyde (**5j**) afforded 60:40 mixtures of *anti*-**6** and *syn*-**6′** *β*-hydroxy sulfides (entries 7 and 8), whereas the reaction of (*S*)-**2** with pivalaldehyde (**5k**) afforded *anti*-**6k** as the only diastereoisomer (>98% de, entry 9). Compounds **6** and **6′** could be isolated by chromatography in enantiomerically pure form.

On the basis of the complete stereoselectivity control exerted by the sulfinyl group on its benzylic position, we assume that **6** and **6′** are epimers at the hydroxylic carbon. To check this assumption, we performed the oxidation of the couple *anti*-**6e** and *syn*-**6′e** (obtained under the conditions of entry 3) with PCC. Only ketone **7** was obtained (Scheme 3), indicating that both isomers only differed in the configuration at the hydroxylic carbon.

TABLE 1. Reactions of (*S*)-2 with Aldehydes 5c−k



entry	aldehyde	R	dr (**6**:**6′**)	yield[a] (%)
1	**5c**	C_6H_5	75:25	56
2	**5d**	*p*-$MeOC_6H_4$	71:29	73
3	**5e**	2-naphthyl	68:32	92
4	**5f**	*p*-CNC_6H_4	70:30	quant
5	**5g**	2,6-di-MeC_6H_3	84:16	70
6	**5h**	2,4,6-tri-$MeOC_6H_2$	100:0	78
7	**5i**	Bu	60:40	74
8	**5j**	^{i}Pr	60:40	54
9	**5k**	^{t}Bu	100:0	60

[a] Isolated yield

SCHEME 3

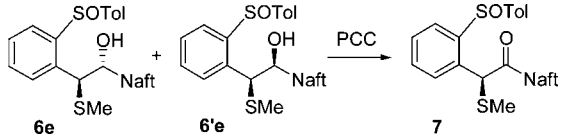
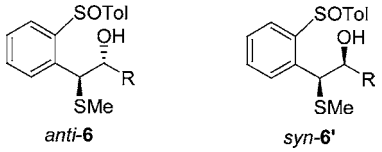


TABLE 2. NMR Parameters of Compounds 6 and 6′ Used for Their Configurational Assignment



compd	$J_{1,2}$ (Hz)	$J_{1,OH}$ (Hz)	compd	$J_{1,2}$ (Hz)	$J_{1,OH}$ (Hz)
6c	9.5	8.5	**6′c**	6.9	2.2
6d	9.1	9.0	**6′d**	7.0	1.1
6e	7.9	9.3	**6′e**	6.5	
6i	8.6	8.4	**6′i**	6.9	2.7
6j	10.1	9.4	**6′j**	6.5	4.4
6h	9.6	9.8			

The *anti* arrangement of the heteroatomic functions assigned to compounds **6c**−**e** and **6h**−**j**, obtained as major epimers in their respective reactions, is based on their ^{1}H NMR parameters. In all of them (Table 2), the value observed for the vicinal coupling constants of their (1)HC−CH(2) fragments ranges between 7.9 and 10.1 Hz, which indicates the predominance of the rotamer with H(1) and H(2) in an antiperiplanar arrangement. Moreover, a very large vicinal coupling constant, $J_{H-O-C-H(1)}$ ($J \geq 8.4$ Hz; see Table 2), is observed for compounds **6**, evidencing a similar arrangement between H(1) and OH. These unusually high values for the coupling constants of the hydroxylic protons suggest they are involved in strong hydrogen bonds.[18] The only possible stereochemistry able to explain the coupling constants measured for compounds **6** is that depicted

(15) See the Experimental Section.

(16) (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2282−2316. (b) Basu, A.; Thayumanauan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 716−738. (c) Toru, T.; Nakamura, S. *Top. Organomet. Chem.* **2003**, 177−216.

(17) Higher reaction times lead to mixtures of epimers.

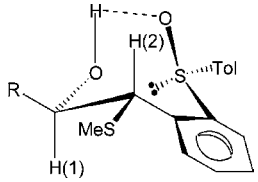
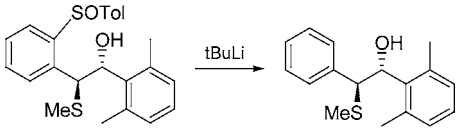


FIGURE 1. Favored conformation for compounds *anti*-**6**.

SCHEME 4



anti-**6g** *anti*-**8g**

in Figure 1, with H(1) adopting the *anti* arrangement with respect to both H(2) and OH, and with the sulfinyl oxygen acting as an acceptor of the hydrogen bond with the hydroxy group. As the configuration of the sulfinyl sulfur should not be affected by the reaction, the absolute configuration of compounds **6** must be (1*R*,2*S*,S*S*).[19] The configurational assignment of the hydroxy thioethers *anti*-**6** not listed in Table 2 is not so clear from their NMR parameters. However, we have done the assignment indicated in Table 1, by assuming similar stereochemical pathways for all these reactions.

By contrast, compounds *syn*-**6′** show $^3J_{1,2}$ values of 6−7 Hz (Table 2), suggesting a significant contribution of rotamers with such protons in *gauche* and *anti* relationships, and $J_{H-O-C-H(1)}$ ranging between 1.1 and 4.4 Hz. The configurational assignment of these diastereoisomers was unequivocally confirmed in the case of *syn*-**6′d** by X-ray analysis.[20]

Compounds **6a**−**k** can be easily transformed into *β*-hydroxy sulfides by C-desulfinylation with organolithium compounds following reported procedures.[21] We have illustrated these transformations by desulfinylation of *anti*-**6g** with ^{t}BuLi[22] (1.8 equiv), which affords the hydroxy sulfide **8g** in 80% yield, with the same optical purity as the precursor (Scheme 4).

The stereochemical outcome of these reactions can be rationalized according to four-membered cyclic transition states **TS-1** and **TS-2**, similar to those proposed for the reactions of other α-sulfinylbenzyl carbanions with different electrophiles (Figure 2).[13a,b,14] They result in the two possible approaches of the aldehyde to the presumably most stable conformation of

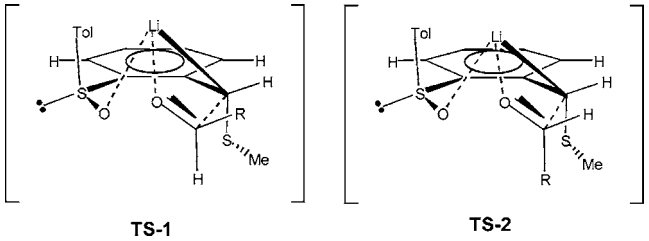


FIGURE 2. Transition states for reactions of (*S*)-**2** with **5c**−**k**.

the carbanion derived from (S)-**2**, which is that depicted in Figure 2. On the basis of the steric interactions, **TS-1** (affording the *anti* compound) must be favored with respect to **TS-2** (yielding the *syn* isomer). This agrees with the increase of the stereoselectivity with the steric size of the aldehyde.

In summary, we have been able to synthesize enantiomerically pure *β*-hydroxy sulfides with the two contiguous stereogenic centers in two steps, reaction of the lithium benzylcarbanion derived from (*S*)-**2** with aliphatic and aromatic aldehydes and subsequent hydrogenolysis of the C−SO bond with ^{t}BuLi.

Experimental Section

General Method. Synthesis of *β*-Hydroxy Sulfides. A solution of *n*-BuLi (1.6 M) in hexane (0.60 mmol, 1.2 equiv) was added over ^{i}Pr$_2$NH (0.89 mmol, 1.8 equiv) in THF (3 mL) at −40 °C. After 15 min of stirring at room temperature, the mixture was cooled at −78 °C, and then a solution of (*S*)-α-(methylthio)-2-(*p*-tolylsulfinyl)toluene [(*S*)-**2**] (0.50 mmol, 1.0 equiv) in THF (2 mL) was added. After 1 min of stirring, the electrophile **4** or **5** (1.0 mmol, 2.0 equiv) dissolved in THF (4 mL) was added at −78 °C. When the reaction was complete (1 min), the mixture was quenched at that temperature with methanol (2 mL). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography.

Data for [1*R*,2*S*,*SS*]-2-(methylthio)-1-(2,4,6-trimethoxy)phenyl-2-[2-(*p*-tolylsulfinyl)phenyl]-1-ethanol (6h): eluent for chromatography, hexane/Et$_2$O/CH$_2$Cl$_2$, 1:2:1; yield 78%; colorless syrup; [α_D^{20}] = −109.6 (*c* 1.2, CHCl$_3$); ^{1}H NMR 7.88−7.86 (m, 1H), 7.63 (dd, 1H, *J* = 7.8 and 1.1 Hz), 7.56−7.54 (m, 1H), 7.37 (dt, 1H, *J* = 7.6 and 1.1 Hz), 7.48 and 7.25 (AA′BB′ system, 4H), 5.45 (dd, 1H, $J_{HO,1}$ = 9.8 Hz, $J_{2,1}$ = 9.6 Hz), 5.28 (d, 1H, *J* = 9.6 Hz), 3.81 (s, 9H), 2.29 (d, 1H, *J* = 9.9 Hz), 2.37 (s, 3H), 1.56 (s, 3H); ^{13}C NMR *δ* 160.9, 158.3, 145.0, 141.0, 140.8, 140.4, 109.3, 131.1, 130.0, 129.7, 129.4, 128.4, 126.6, 125.3, 90.7, 90.8, 69.9, 55.5, 55.2, 21.3, 14.3; HRMS *m*/*z* calcd for C$_{25}$H$_{26}$O$_4$S$_2$ (M$^+$ − H$_2$O) 454.1273, found 454.1283.

General Method. Oxidation of *β*-Hydroxy Sulfides to Ketones. A mixture of epimeric alcohols **6e** + **6′e** (20 mg, 0.048 mmol, 1 equiv) was dissolved in dry CH$_2$Cl$_2$ (2 mL), and PCC (15.7 mg, 0.073 mmol, 1.5 equiv) was added. The mixture was stirred at room temperature for 2 h. The solvent was partially evaporated, and the residue was purified by flash column chromatography (hexane/Et2O/CH$_2$Cl$_2$, 2:1:1) to give pure 2-(methylthio)-1-(2-naphthylphenyl)-2-[2-(*p*-tolylsulfinyl)phenyl]ethanone (**7**) in 50% yield: colorless syrup; [α_D^{20}] = −74.0 (*c* 0.2, CHCl$_3$); ^{1}H NMR *δ* 8.39 (s, 1H), 7.92−7.81 (m, 5H), 7.65−7.48 (m, 5H), 7.28 (AA′BB′ system, 2H, *J* = 8.3 Hz), 6.97 (d, 2H, *J* = 8.3 Hz), 6.20 (s, 1H), 2.19 (s, 3H), 2.12 (s, 3H).

General Method for C−S Desulfinylation. To a stirred solution of **6g** (43.6 mg, 0.106 mmol, 1 equiv) in THF (2 mL) was added ^{t}BuLi (127 *μ*L, 0.19 mmol, 1.5 M in hexane, 1.8 equiv) at −78 °C. When the reaction was complete (5 min), the mixture was hydrolyzed with saturated aqueous NH$_4$Cl solution (2 mL) and

(18) In the absence of hydrogen bonds, the quick interchange of the OH protons (absence of coupling) or the free rotation around the C−O bonds determines average values for the vicinal coupling constants (4−6 Hz). For references using these criteria in configurational assignment see: (a) Kingsbury, C. A.; Aerbach, R. A. *J. Org. Chem.* **1971**, *36*, 1737−1742 and references therein. (b) Brunet, E.; García Ruano, J. L.; Hoyos, M. A.; Rodríguez, J. H.; Prados, P.; Alcudia, F. *Org. Magn. Reson.* **1983**, *21*, 643. (c) Brunet, E.; García Ruano, J. L.; Rodríguez, J. H.; Alcudia, F. *Tetrahedron* **1984**, *40*, 4433. (d) Carretero, J. C.; García Ruano, J. L.; Martínez, M. C.; Rodríguez, J. H. *Tetrahedron* **1985**, *41*, 2419. (e) Carreño, M. C.; Carretero, J. C.; García Ruano, J. L.; Rodríguez, J. H. *Tetrahedron* **1990**, *46*, 5649.

(19) As additional data reinforcing the configurational assignment, the *anti* isomers exhibit higher δ_{OH} but lower δ_{Me} values than their corresponding *syn* epimers, as had been previously observed for similar compounds (see ref 13d).

(20) X-ray data are available in the Supporting Information.

(21) Clayden, J.; Mitjans, D.; Youssef, L. H. *J. Am. Chem. Soc.* **2002**, *124*, 5266−5267.

(22) The use of Raney nickel for desulfinylation also affects the benzylic C−S bond.

extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexane/Et_2O/CH_2Cl_2, 2:1.5:1.5) to give pure **8g** in 80% yield: colorless syrup; $[\alpha_D^{20}] = -31.3$ (*c* 0.2, $CHCl_3$); ^{1}H NMR 7.54−7.40 (m, 4H), 7.31−7.27 (m, 1H), 7.15−7.11 (m, 1H), 7.06−7.04 (m, 2H), 5.46 (d, 1H, $J = 9.8$ Hz), 4.41 (d, 1H, $J = 9.8$ Hz), 2.60 (s, 6H), 2.43 (s, 1H), 1.67 (s, 3H); ^{13}C NMR δ 141.5, 140.0, 137.2, 136.6, 129.0, 128.8, 128.6, 127.7, 126.2, 74.4, 56.1, 22.6, 15.1.

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Supporting Information Available: Experimental data of compounds **4**, **6a**−**k** (except for **6h**), and **6′c**−**j**, NMR spectra of all compounds, and X-ray data of compound **6′d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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