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Directed *Ortho* Metalation−Cross Coupling Strategies. *N*-Cumyl Arylsulfonamides. Facile Deprotection and Expedient Route to 7- and 4,7-Substituted Saccharins[⊥]

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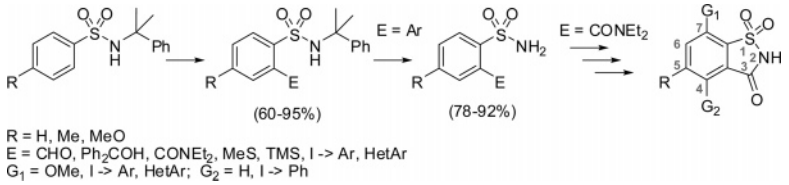

By using the powerful *N*-cumylsulfonamide directed metalation group (DMG), a series of 2-substituted derivatives were prepared according to the directed *ortho* metalation (D*o*M) tactic (Table 1). Mild conditions for *N*-decumylation and other simple transformations of the products have been achieved (Scheme 2). The 3-silyloxy sultam **12** undergoes further D*o*M to give formyl, thiomethyl, iodo, and amide derivatives **13a**−**g** of potential value for saccharin synthesis (Table 2). An effective route to target 7-aryl saccharins via Suzuki cross coupling (Table 3) followed by further metalation−carbamoylation and cyclization (Table 5) is described. 4,7-Disubstituted saccharins have been obtained by similar sequences (Scheme 3). Mild TFA-mediated *N*-decumylation furnishes substituted primary arylsulfonamides (Table 4).

Introduction

Since the discovery of saccharin,[1] the 1,2-dihydrobenzo[*d*]-isothiazole 1,1-dioxide (sultam) and related 1,2-dihydrobenzo-[*d*]isothiazol-3-one 1,1-dioxide (saccharin) ring systems have been viewed with considerable interest, unsurprisingly, in the pharmaceutical[2] and flavor[3] industries but, as perhaps less appreciated, also in the polymer[4] and metal coordination[5] fields. Interest was further enhanced by the discovery of a human leukocyte elastase inhibitor, KAN 400473[6] (Chart 1), used for treatment of emphysema and by reports of structural variations, e.g., WIN 63294.[7] More recently, 4,7-substituted saccharins appear as substructures in the Merck carbapenem antibacterial agents.[8] The discovery of the anti-inflammatory properties of the 4-hydroxy-1,2-benzothiazine 1,1-dioxide (oxicam) ring system,[9] constituting a ring-expanded saccharin, further stimulated synthetic activity in this area.

As illustrated by the commercial medicinal agents (Chart 1), *N*-substitution and benzene moiety functionalization are significant components in conceptualizing approaches to the

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⊥ This paper is dedicated to Steve Ley, an outstanding chemist, a wise advisor, and a bon vivant.

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(1) Fahlberg, C.; Remsen, I. *Chem. Ber.* **1879**, *12*, 469−473.

(2) Wilkening, R. R.; Ratcliffe, R. W.; Wildonger, K. J.; Cama, L. D.; Dykstra, K. D.; DiNinno, F. P.; Blizzard, T. A.; Hammond, M. L.; Heck, J. V.; Dorso, K. L.; St. Rose, E.; Kohler, J.; Hammond, G. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 673−678. Sunramanyam, C.; Bell, M. R. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 733−736.

(3) Hettler, H. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Burton, A. J., Eds.; Academic Press: New York, 1973; Vol. 3, p 233.

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(8) Merck & Co Inc., 126 East Lincoln Ave., Rahway, NJ, 07065, U.S. Patent No. WO9810661.

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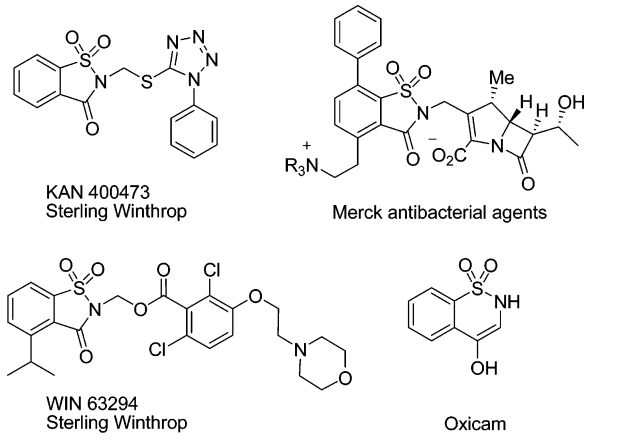
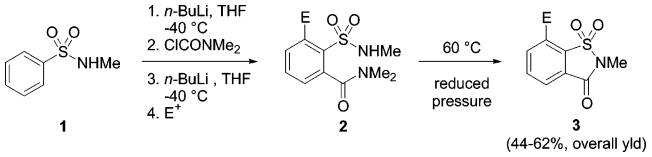
CHART 1. Bioactive Saccharin Derivatives



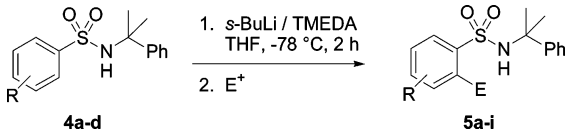
SCHEME 1. Synthesis of 7-Substituted *N*-Methyl Saccharins



saccharin ring system.[10] Whereas 5- and 6-substituted saccharins are readily accessed via electrophilic substitution regimens,[10] 7- and 4,7-substituted derivatives lacked a general approach until the work of Proudfoot,[10a] who reported an elegant one-pot approach to 7-substituted derivatives **3** based on two successive directed *ortho* metalation (D*o*M) reactions starting from secondary sulfonamide **1**, the second of which takes advantage of the more powerful sulfonamide directed metalation group (DMG) effect to lead to the regioselective formation of **2** (Scheme 1).[11] The drawbacks of this route are the modest yields and, significantly, the de facto formation of the *N*-methyl saccharin **3** that precludes further functionalization, a process of value for drug analogue synthesis. The work of Hlasta,[6,10b] which has been utilized in the synthesis of many pharmaceutically important saccharins (Chart 1), provides a route to *N*-unsubstituted saccharins but does not permit variable functionalization of the 7-position. Furthermore, few routes to 4,7-disubstituted saccharins have been reported and developed.[12]

As part of our continuing efforts to broaden the scope of new D*o*M strategies,[13] a rekindling of interest in sulfonamide metalation,[14] and the discovery of the *N*-cumyl DMG for amides, *O*-carbamates, and sulfonamides,[15] we report on (a) the generalization and extension of the reported[15] *N*-cumylsulfonamide D*o*M chemistry (Table 1), (b) the D*o*M chemistry of the derived 2,3-dihydrobenzo[*d*]isothiazol-3-ol **12**, which provides 7-substituted saccharins and benzoisothiazines (Scheme 2 and Table 2), (c) the Suzuki cross coupling chemistry of the D*o*M-derived iodo arylsulfonamides for the construction of biaryl sulfonamides (Table 3),[14] and (d) new combined D*o*M−Suzuki protocols for the synthesis of both 7-aryl and 4,7-diaryl-substituted saccharin derivatives (Table 5 and Scheme 3). The overriding feature of the described methodology is the provision of mild conditions for conversion of *N*-cumylsulfonamides to primary sulfonamides (Table 4), allowing the retention of sensitive functionality.[17]

TABLE 1. D*o*M Synthesis of 2-Substituted *N*-Cumyl Arylsulfonamides



entry	product	R	E^+	E	yield, %, **5**
1	**5a**	H	DMF	CHO	87
2	**5b**	H	Ph_2CO	Ph_2COH	95
3	**5c**	H	$ClCONMe_2$	$CONMe_2$	79
4	**5d**	H	TMSCl	TMS	60
5	**5e**	H	MeSSMe	SMe	92
6	**5f**	H	I_2	I	88
7	**5g**	4-Me	I_2	I	84[a]
8	**5h**	2-MeO	$ClCONEt_2$	$CONEt_2$	75[a]
9	**5i**	4-MeO	I_2	I	64[a]

[a] Reactions carried out at 0 °C with *n*-BuLi as base for 1 h.

Results and Discussion

To begin, reinforcement and extension of the preliminary findings[15] concerning the powerful *N*-cumylsulfonamide DMG was undertaken. Thus treatment of compounds **4a**−**d**, conveniently prepared by the reaction of arylsulfonyl chlorides and cumylamine (see the Supporting Information), with selected electrophiles gave 2-substituted arylsulfonamides **5a**−**i** mostly in excellent yields (Table 1). *Ortho* rather than benzylic deprotonation of **5g** (entry 7) was assured from results of

(9) Lombardino, J. G.; Wiseman, E. H. *Med. Res. Rev.* **1982**, *2*, 127−152.

(10) (a) Proudfoot, J. R.; Patel, U. R.; Dyatkin, A. B. *J. Org. Chem.* **1997**, *62*, 1851−1853. (b) Hlasta, D. J.; Bell, M. R.; Court, J. J.; Cundy, K. C.; Desai, R. C.; Ferguson, E. W.; Gordon, R. J.; Kumar, V.; Maycock, A. L.; Subramanyam, C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 331−336. (c) Zlotin, S. G.; Kislitsin, P. G.; Podgursky, A. I.; Samet, A. V.; Semenov, V. V. *J. Org. Chem.* **2000**, *65*, 8439−8443. (d) Xu, L.; Katohgi, M.; Togo, H.; Yamaguchi, K.; Yokoyama, M. *Tetrahedron* **1999**, *55*, 14885−14900. (e) Burri, K. F. *Helv. Chim. Acta* **1990**, *73*, 69−80. (f) Loev, B.; Kormendy, M. *J. Org. Chem.* **1962**, *27*, 2448−2452.

(11) The hierarchy of the two DMGs agrees with general observations based on inter- and intramolecular experiments. For reviews, see: Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 330−367. Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206−2225. Macklin, T.; Snieckus, V. In *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Vol. 1, pp 106−118.

(12) E.g., for the oxidation of 4,7-substituted benzo[*d*]isothiazole, see: Becke, F.; Hagen, H. *Justus Liebigs Ann. Chem.* **1969**, *729*, 146−151. For inverted metalation of an appropriate carboxamide, see: Hlasta, D. J.; Court, J. J.; Desai, R. *Tetrahedron Lett.* **1991**, *32*, 7179−7182.

(13) (a) Cai, X.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2293−2295. (b) Macklin, T. K.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2519−2522. (c) Zhao, Z.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2523−2526.

(14) MacNeil, S. L.; Familoni, O. B.; Snieckus, V. *J. Org. Chem.* **2001**, *66*, 3662−3670.

(15) Metallinos, C.; Nerdinger, S.; Snieckus, V. *Org. Lett.* **1999**, *1*, 1183−1186.

(16) For reviews on this methodology, see: Anctil, E. J. G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150−160. Anctil, E. J. G.; Snieckus, V. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Diederich, F., de Meijere, A., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 761−813.

(17) Normally, harsh conditions are required for dealkylation of *N*-alkylsulfonamides, e.g., potassium superoxide: Park, K. H.; Lee, J. B. *Synth. Commun.* **1992**, *22*, 1061. Sonochemical hypervalent iodine: Katohgi, M.; Togo, H. *Tetrahedron* **2001**, *57*, 7481−7486. Katohgi, M.; Yokoyama, M.; Togo, H. *Synlett* **2000**, 1055. Photolysis: Abad, A.; Mellier, D.; Pète, J. P.; Pertella, C. *Tetrahedron Lett.* **1971**, *47*, 4555−4558. For a recent method with periodic acid and catalytic chromium(III) acetate hydroxide allowing mono- and di-*N*-dealkylation even in the presence of aryl TMS substitution, see: Xu, L.; Zhang, S.; Trudell, M. L. *Synlett* **2004**, *11*, 1901−1904.

SCHEME 2. Modification of 2-Substituted *N*-Cumyl Arylsulfonamides

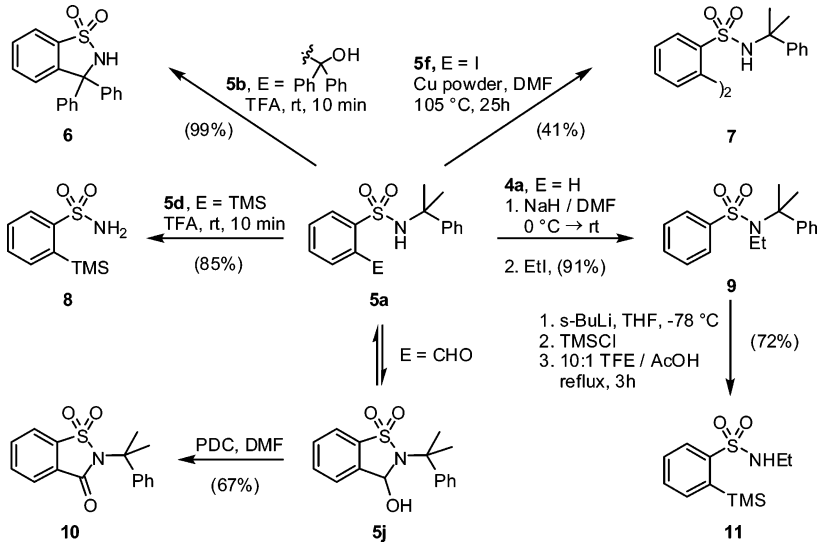
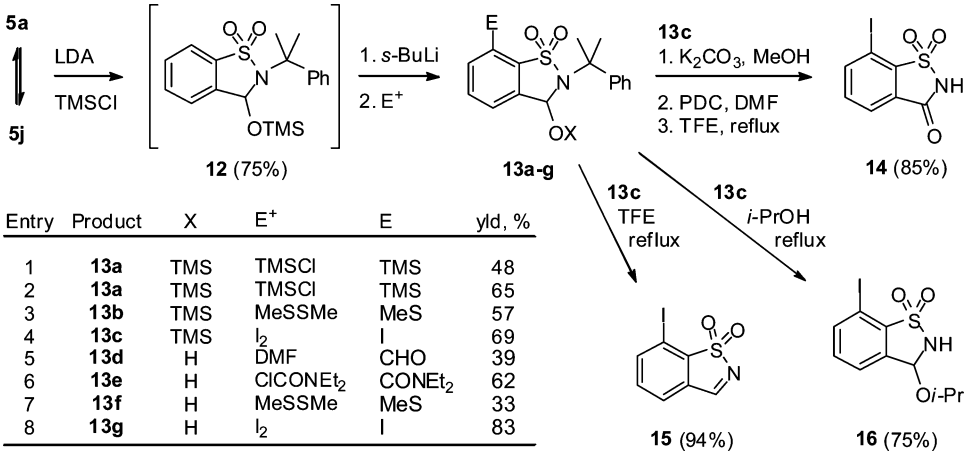


TABLE 2. DoM Chemistry of Silylated Carbinolsulfonamide 5a:5j (E = CHO)



Entry	Product	X	E^+	E	yld, %
1	**13a**	TMS	TMSCl	TMS	48
2	**13a**	TMS	TMSCl	TMS	65
3	**13b**	TMS	MeSSMe	MeS	57
4	**13c**	TMS	I_2	I	69
5	**13d**	H	DMF	CHO	39
6	**13e**	H	$ClCONEt_2$	$CONEt_2$	62
7	**13f**	H	MeSSMe	MeS	33
8	**13g**	H	I_2	I	83

previous studies.[14] Introduction of the *N*,*N*-methyl and *N*,*N*-diethyl carbamoyl DMGs to give **5c**,**h** (entries 3 and 8) proceeded in high yield, similar to that achieved by Proudfoot[10a] for the formation of the *N*,*N*-dimethyl derivative in his corresponding system.

To explore reactivity that parallels previous work on *N*-Me and *N*-phenyl sulfonamides[18] and to show the value of the hydrolytic lability of the *N*-cumyl group, a number of simple transformations were carried out (Scheme 2). Thus, Ullmann homocoupling of 2-iodo derivative **5f** produced the biaryl bisulfonamide **7** in modest yield. Treatment of the tertiary carbinol **5b**, obtained by benzophenone quench, with TFA at room temperature for minutes led in quantitative yield directly to the decumylated sultam **6**.[19] To show the value of the mild decumylation conditions on sensitive substrates, the 2-TMS secondary sulfonamide **5d** and the corresponding tertiary sulfonamide **9**, prepared by ethylation, and after metalation-silylation, were treated under TFA and even milder TFE (pK_a = 12.43)[20]−HOAc (10%) conditions respectively to afford decumylated products **8** and **11**, thus confirming the ability to retain TMS[21] for further potential synthetic use.[22] The 2-formyl derivative **5a**, existing in equilibrium with the corresponding cyclic 2,3-dihydrobenzo[*d*]isothiazol-3-ol 1,1-dioxide **5j** (3:1 **5a**:**5j** by ^{1}H NMR (see the Experimental Section), was easily oxidized into the *N*-cumyl saccharin **10**.

The recognition that saccharins undergo attack at the carbonyl by organolithiums[23] provided the incentive to take advantage of the ring-chain tautomerism **5a**:**5j** process for potential further DoM chemistry studies (Table 2). Treatment with 2 equiv of *s*-BuLi/TMEDA gave a complex mixture, presumably owing

(18) Watanabe, H.; Gay, R. L.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 900−903. Watanabe, H.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 4278−4279. Watanabe, H.; Mao, C. L.; Barnish, I. T.; Hauser, C. R. *J. Org. Chem.* **1969**, *34*, 919−926. Watanabe, H.; Mao, C. L.; Hauser, C. R. *J. Org. Chem.* **1969**, *34*, 1786−1791.

(19) Roberts, C. W.; McBee, E. T.; Hathaway, C. E. *J. Org. Chem.* **1956**, *21*, 1369−1370.

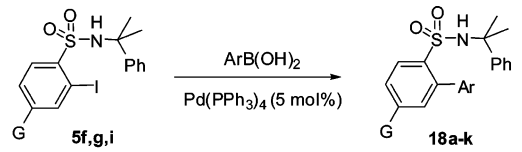
(20) Compound **6** was obtained in 94% yield over two steps from **5b** compared to the two-step 79% yield obtained originally by Hauser using more vigorous HBr cyclization conditions to afford the corresponding *N*-methyl sultam derivative.[18]

(21) We have conveniently removed aryl TMS and TES under refluxing TFA conditions; see: (a) Reed, M. A.; Chang, M. T.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2297−2300. (b) Wang, W.; Snieckus, V. *J. Org. Chem.* **1982**, *57*, 424−426.

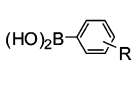
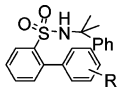
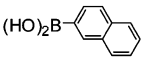
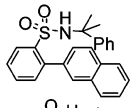
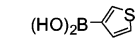
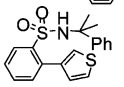
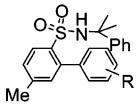
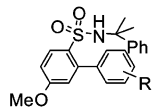
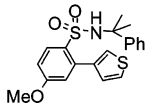
(22) For example, in electrophile-induced ipso desilylation chemistry, see ref 13c.

(23) Porter, N. A.; Carter, R. L.; Mero, C. L.; Roepel, M. G.; Curran, D. P. *Tetrahedron* **1996**, *52*, 4181−4198.

TABLE 3. Synthesis of 18a−k by Suzuki Cross Coupling



5f (G = H), **5g** (G = Me), **5i** (G = MeO)

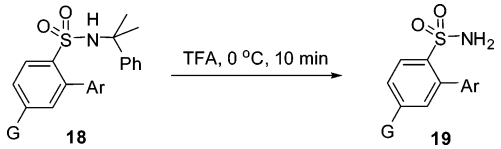
Entry	SM (**5**)	$ArB(OH)_2$ (**17**)[a]	Cond[b]	Product (**18**)	yld, %[c]
					
1	5f	**17a** (R = H)	A	**18a** (R = H)	76
2	5f	**17b** (R = 2,3-diMe)	B	**18b** (R = 2,3-diMe)	80
3	5f	**17c** (R = 2-$CONEt_2$)	A	**18c** (R = 2-$CONEt_2$)	57
4	5f	**17d** (R = 3,5-diCl)	D	**18d** (R = 3,5-diCl)	74
5	5f	 **17e**	C	 **18e**	75
6	5f	 **17f**	B	 **18f**	95
					
7	5g	**17a**	B	**18g** (R = H)	72
8	5g	**17a**	C	**18g** (R = H)	96
9	5g	**17b**	A	**18h** (R = 2,3-diMe)	70
					
10	5i	**17a**	B	**18i** (R = H)	84
11	5i	**17g** (R = 4-CHO)	C	**18j** (R = 4-CHO)	97
12	5i	**17f**	C	 **18k**	80

[a] 2-$MeOC_6H_4B(OH)_2$ gave homocoupled product in 67% yield under conditions A. [b] A: K_3PO_4, DMF, 100 °C. B: aq Na_2CO_3, THF, 70 °C. C: aq Cs_2CO_3, THF, 70 °C. D: aq Na_2CO_3, DME, 90 °C. [c] Isolated and purified product.

to the electrophilicity of the open-chain aldehyde **5a**, which is the predominant ring−chain tautomer under these conditions.[24] Although LDA-mediated silylation furnished, in good yield, the 3-silyloxy sultam **12**, which was chromatographed and spectroscopically characaterized, this compound underwent slow desilyation over time to give **5a**:**5j**. However, *s*-BuLi/TMEDA (1 equiv) metalation conditions followed by quench with TMSCl afforded the 7-TMS product **13a** in modest yield (Table 2, entry 1). The site of substitution was verified by 2D NMR (see the Supporting Information). The yield of this reaction was considerably improved by use of 2 equiv of *s*-BuLi/TMEDA (entry 2), conditions which were then applied for the introduction of other electrophiles to afford products **13b**−**g** (entries 3−8). In several cases, the workup was effected with methanolic K_2CO_3, which furnished the desilylated products **13d**−**g** (entries 5−8). Three additional transformations of **13c** were carried out: K_2CO_3 desilylation, PDC oxidation, and TFE-induced decumylation gave **14** while direct TFE treatment resulted in the formation of benzoisothiazole **15**. Simple treatment of **13c** under refluxing *i*-PrOH conditions funished

(24) Metallinos, C. Ph.D. Thesis, Queen's University, 2001.

TABLE 4. *N*-Decumylation: Synthesis of Primary Arylsulfonamides 19a−e



SM (**18**)[a]	product (**19**)	G	Ar	yield,[b] %
18b	**19a**	H	2,3-Me_2-C_6H_3	92
18e	**19b**	H	2-naphthyl	83
18g	**19c**	Me	Ph	90
18i	**19d**	MeO	Ph	91
18j	**19e**	MeO	4-$OHCC_6H_4$	78

[a] For structures, see Table 3. [b] Isolated and purified product.

the hemiaminal **16**. All products constitute simple but unknown and potentially valuable 7-iodo derivatives.

In view of the lability of 7-iodo *O*-silyl 2,3-dihydrobenzo-[*d*]isothiazol-3-ol **13c**, the D*o*M−Suzuki cross coupling strategy for the preparation of 7-substituted saccharins was inverted: cross coupling of the 2-iodo *N*-cumyl arylsulfonamides **5f**,**g**,**i** followed by metalation and *N*,*N*-diethylcarbamoyl chloride quench prior to cyclization to the saccharins. The Suzuki reaction on **5f**,**g**,**i** (Table 3) was carried out under several optimized conditions A−D, of which the use of 2 equiv of Cs_2CO_3 in a biphasic medium (C) produced the best yields under the shortest reaction times. Very good to excellent yields of products were achieved for a range of boronic acids **17a**−**g** and led to unsubstituted (entries 1, 7, 8, and 10), alkylated (entries 2 and 9), chlorinated (entry 4), and formylated (entry 11) biaryl *N*-cumylsulfonamides. Unhindered naphthalene 2-boronic acid (**17e**) also underwent smooth coupling (entry 5). Interestingly, 2-anisylboronic acid gave only a homocoupling product (footnote a).[25] Modest hindrance effects (entries 2, 3, and 9) appear to be of minor consequence to the yields obtained in the reaction. One (commercial) heterocylic boronic acid (**17f**) underwent smooth coupling reactions to give **18f** and **18k** (entries 6 and 12); both of these heterobiaryl sulfonamides as well as the corresponding sulfonamide amide **18c** (entry 3) invite inquiry regarding the regioselectivity of further D*o*M chemistry.

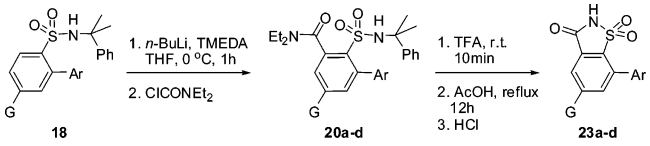
N-Decumylation of selected biaryl sulfonamides **18b**,**e**,**g**,**i**,**j** proceeded under the mild TFA/0 °C/10 min conditions to the corresponding primary sulfonamides **19a**−**e** (Table 4). Differentially *N*-alkylated sulfonamides may be obtained via this route or via alkylation prior to D*o*M chemistry (Scheme 2).

The sequences depicted in Table 5 and Scheme 3 conclude the goal of establishing viable routes to 4- and 4,7-substituted saccharin derivatives. Thus *n*-BuLi/TMEDA metalation of selected biaryl *N*-cumylsulfonamides **18a**, **18e**, **18g**, and **18i** followed by *N*,*N*-diethylcarbamoyl chloride quench gave the expected amide sulfonamides **20a**−**d** (Table 5). The metalation regiochemistry of **18g** was expected on the basis of the previous results of *p*-tolylsulfonamide metalation (Table 1) while that of **18i** is foretold by the order of SO_2NHR > OMe DMG power.[11] Mostly without isolation, these were conveniently transformed directly by mild TFA decumylation followed by

(25) Under similar conditions, 2-anisylboronic acid has been reported to undergo homocoupling more efficiently than all the other boronic acids tested; see: Lei, A.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 2525−2528.

(26) Desai, R. C.; Hlasta, D. J.; Monsour, G.; Saindane, M. T. *J. Org. Chem.* **1994**, *59*, 7161−7163.

TABLE 5. Synthesis of 7-Substituted Saccharins 23a−d



	product (yield, %)[b]			
SM (**18**)[a]	**20**	**23**	G	Ar
18a	**20a** (99)	**23a** (90)	H	Ph
18e	**20b**[c]	**23b** (57)[d]	H	2-naphthyl
18g	**20c**[c]	**23c** (42)[d]	Me	Ph
18i	**20d** (78)[c]	**23d** (88)	MeO	Ph

[a] See footnote *a*, Table 4. [b] Isolated and purified products. [c] Used directly after column chromatography without characterization in the next step. [d] Yield over two steps.

HOAc treatment[26] into the *N*-unsubstituted saccharins **23a−d** in modest to excellent yields.

The sequence leading to 4,7-disubstituted saccharins **23e**,**f** (Scheme 3) was initiated by *n*-BuLi/TMEDA−iodination sequence of **20a** and **5h** to give the corresponding iodo derivatives **21a** and **21b**, respectively. Suzuki cross coupling with phenylboronic acid under the Na_2CO_3 conditions, as previously established (Table 4), afforded the tetrasubstituted aromatics **22a** and **22b**, which, when subjected to the above decumylation and cyclization conditions, delivered the 4,7-disubstituted saccharins **23e** and **23f** respectively in good overall yields. The depicted methodology conceptualized by schematic **24** may be considered in general context whereby other than carbamoyl DMGs (step 2) and electrophilic halogen (steps 1 and 3) are introduced leading potentially to the construction of differentially and contiguously substituted *p*-teraryls.

Conclusions

In summary, the D*o*M chemistry of the *N*-cumylsulfonamide DMG has been generally demonstrated (Table 1) and the mild conditions for *N*-decumylation have been illustrated (Scheme 2 and Table 4). While regioselective C-7 D*o*M reactions on the 3-silyloxy sultam **12** may be achieved and lead to 7-iodo benzoisothiazole and saccharin derivatives (Table 2) which could be used for Suzuki cross coupling to 7-substituted saccharins, the inversion of the two steps—Suzuki reaction (Table 3) followed by carbamoylation and cyclization (Table 5)—provides a more efficient route to the target molecules **23a−d**. Taking advantage of the introduced *N*,*N*-diethylcarbamoyl DMG then allows the construction of exemplary 4,7-disubstituted saccharins **23e**,**f** (Scheme 3). As is generally observed, new results in the D*o*M area, although of some vintage for the sulfonamide case,[18] provide contemplation for further useful anionic aromatic chemistry (e.g., compounds **18c**,**f**,**k** and schematic **24**) as a function of the interest and need of the synthetic chemist.

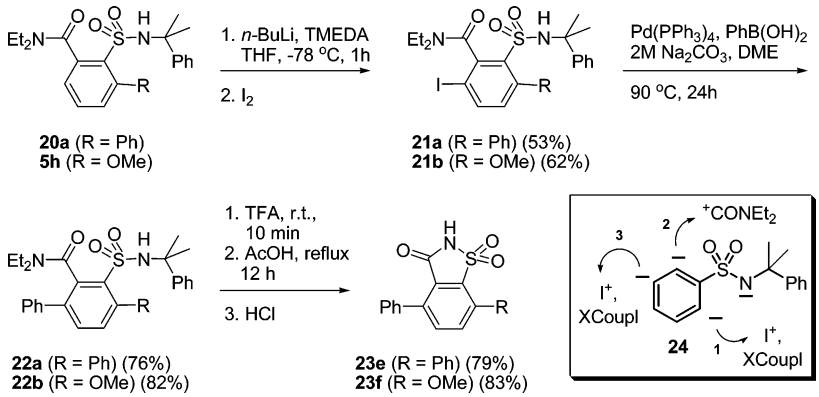
Experimental Section

D*o*M of *N*-Cumyl Arylsulfonamides: General Procedure 1. A flame-dried, argon-flushed, round-bottomed flask containing a solution of an appropriate sulfonamide **4a−d** (1 mmol) and TMEDA (2.2 mmol) in THF (10 mL) cooled to −78 °C was treated dropwise with a solution of *s*-BuLi (2.2 mmol, 1.17−1.38 M in cyclohexane). The resulting yellow solution was allowed to stir for 2 h, the electrophile (1.2 mmol) was added dropwise, and the mixture was allowed to warm slowly to room temperature. Saturated aqueous NH_4Cl (10 mL) was added, the mixture was transferred to a separatory funnel with EtOAc, and the organic phase was separated. The aqueous phase was extracted with EtOAc (2 × 10 mL) and the organic extracts were combined, washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (hexanes:EtOAc).

2-Formyl-*N*-(2-phenylpropan-2-yl)benzenesulfonamide (5a). This compound was prepared according to General Procedure 1 with the following materials: **4a** (1.10 g, 4 mmol), TMEDA (1.33 mL, 8.8 mmol), THF (40 mL), *s*-BuLi (6.67 mL, 1.32 M in cyclohexane, 8.8 mmol), and DMF (0.37 mL, 4.8 mmol). Column chromatography (3:1 hexanes:EtOAc) yielded **5a** (1.05 g, 87%) as a pale yellow solid: mp 115−118 °C; IR υ_{max} (KBr) 3264, 3021, 2988, 2961, 2879, 2780, 1702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 3:1 ratio with cyclic form **5j**) δ 10.30 (s, 0.75H, C**H**O), 7.85−6.98 (m, 9H, Ar**H**), 6.37 (s, 0.75H, N**H**), 5.66 (br s, 0.25H, ArC**H**), 3.49 (br s, 0.25H, O**H**), 2.07−2.05 (m, 0.75H, C**H**$_3$), 1.67 (s, 2.25H, C**H**$_3$) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$, 3:1 ratio with cyclic form **5j**) δ 191.4, 144.6, 143.4, 142.1, 135.7, 135.6, 133.4, 133.1, 132.5, 132.4, 131.8, 130.5, 129.3, 128.4, 127.7, 127.4, 126.9, 126.1, 125.6, 124.8, 120.2, 81.0, 62.0, 58.4, 29.8, 28.9, 28.5 ppm; EIMS (*m*/*z* (%)) 303 [M^+] (1), 288 (100), 169 (79), 119 (97), 105 (41), 91 (49) 77 (47); HRMS (EI) calcd for $C_{16}H_{17}NO_3S$ [M^+] 303.0929, found 303.0929.

Decumylation of *N*-Cumyl Arylsulfonamides: General Procedure 2. 2-Trimethylsilylbenzenesulfonamide (8). To compound **5d** (103 mg, 0.296 mmol) was added ice-cooled TFA (2 mL) and the resulting solution was stirred at room temperature for 10 min before the solvent was removed in vacuo. Recrystallization afforded **8** as colorless crystals (58 mg, 85%): 140−155 °C (sublimation) (hexanes:EtOAc); IR (KBr) υ_{max} 3380, 3251, 3070, 3057, 2949, 2898, 1560, 1332, 1160 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 8.09−8.04 (m, 1H), 7.79−7.75 (m, 1H), 7.60−7.52 (m, 2H), 6.48 (br s, 2H), 0.39 (s, 9H) ppm; ^{13}C NMR (50.3 MHz, acetone-d_6) δ 150.1, 138.5, 136.8, 131.6, 130.3, 128.2, 1.3 ppm; CIMS (*m*/*z* (%))

SCHEME 3. Synthesis of 4,7-Disubstituted Saccharins 22a,b



230 $[MH]^+$ (2), 214 (100); HRMS (EI) calcd for $C_8H_{12}NO_2SiS$ $[M - CH_3]^+$ 214.0358, found 214.0376.

***N,N′*-Di(2-phenylpropan-2-yl)-biphenyl-2,2′-disulfonamide (7).** To a stirred solution of iodide **5f** (404 mg, 1.01 mmol) in DMF (20 mL) was added activated Cu powder (1.27 g, <10μ, 20 mmol), and the mixture was heated under argon at 110 °C for 25 h. The mixture was cooled and subjected to filtration through Celite. The filtrate was diluted with water (100 mL) and the whole was extracted with EtOAc (3 × 20 mL), and the organic extracts were combined, washed with water (3 × 50 mL), washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (3:1 hexanes:EtOAc) yielded **7** (114 mg, 41%) as a viscous colorless oil: IR (NaCl, neat) υ_{max} 3277, 3059, 3028, 2981, 2932, 1320, 1149 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.69−7.64 (m, 2H), 7.38−7.13 (m, 16H), 5.01 (s, 2H), 1.66 (s, 6H), 1.60 (s, 6H) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 145.5, 140.3, 132.0, 130.7, 128.8, 128.1, 127.0, 125.5, 107.5, 59.3, 30.1, 29.9 ppm; FABMS (*m/z* (%)) 533 $[M - CH_3]^+$ (6), 415 (40), 217 (68), 168 (44), 152 (49), 134 (41), 118 (63) 104 (100); HRMS calcd for $C_{29}H_{29}N_2O_4S_2$ $[M - CH_3]^+$ 533.1569, found 533.1559.

2-(2-Phenylpropan-2-yl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-Dioxide (10). Compound **5a** (2.30 g, 8.2 mmol) was dissolved in DMF (33 mL) under argon at room temperature and the resulting solution was stirred and treated with PDC (6.20 g, 16 mmol). After 21 h, water (160 mL) was added, the mixture was transferred to an extraction funnel with EtOAc, and the organic phase was separated. The aqueous phase was extracted with EtOAc (2 × 50 mL), and the organic extracts were combined, washed with water (2 × 50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (toluene/EtOAc 46:1) yielded **10** (1.62 g, 67%) as a colorless viscous oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.92−7.81 (m, 3H), 7.78−7.73 (td, J = 7.4, 1.3 Hz, 1H), 7.51−7.47 (m, 2H), 7.38−7.32 (m, 2H), 7.29−7.24 (m, 1H), 2.11 (s, 6H). Spectroscopic data were in agreement with those reported.[15]

2-(2-Phenylproan-2-yl)-3-(trimethylsilyloxy)-2,3-dihydrobenzo[*d*]isothiazole 1,1-Dioxide (12). In a flame-dried, argon-flushed flask containing diisopropylamine (0.61 mL, 4.3 mmol) in THF (20 mL) was added dropwise at 0 °C *n*-BuLi (1.7 mL, 2.52 M, 4.3 mmol) followed by TMSCl (1.1 mL, 8.6 mmol). A solution of **5a** (1.2 g, 3.9 mmol) in THF (10 mL) was then added dropwise and the whole was warmed to room temperature and stirred for 22 h. Saturated aqueous NH_4Cl (20 mL) was added and the mixture was transferred to an extraction funnel with Et_2O. The organic phase was separated and the aqueous phase was extracted with Et_2O (2 × 10 mL), then the organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (22:3 hexanes:EtOAc) yielded **12** (1.1 g, 75%) as a beige waxy solid that underwent desilylation over several days to starting **5a**: ^1H NMR (200 MHz, $CDCl_3$) δ (uncorrected) 7.78−7.74 (m, 1H), 7.62−7.49 (m, 4H), 7.41−7.25 (m, 4H), 5.80 (s, 1H), 2.05 (s, 6H), −0.07 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.8, 136.5, 136.0, 132.5, 130.4, 128.4, 127.4, 126.4, 124.5, 120.8, 81.7, 62.3, 31.2, 27.5, 0.8 ppm.

7-Iodo-2-(2-phenylpropan-2-yl)-3-(trimethylsilyloxy)-2,3-dihydrobenzo[*d*]isothiazole 1,1-Dioxide (13c). This compound was prepared according to General Procedure 1 with the following materials: **12** (0.34 g, 0.91 mmol), TMEDA (0.27 mL, 1.8 mmol), THF (9 mL), *s*-BuLi (1.3 mL, 1.38 M, 1.8 mmol), and I_2 (0.51 g, 2.0 mmol, in 4.5 mL of THF). Column chromatography (22:3 hexanes:EtOAc) yielded **13c** (0.31 g, 69%) as a colorless solid: mp 104−105 °C; IR (KBr) υ_{max} 2972, 2951, 1304, 1182, 1144, 1029, 869, 556 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95−7.93 (dd, 1H, J = 1.2, 7.3 Hz), 7.53−7.51 (m, 2H), 7.39−7.35 (m, 2H), 7.32−7.23 (m, 3H), 5.65 (s, 1H), 2.04 (s, 6H), −0.07 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 140.9, 138.9, 138.8, 133.2, 128.4, 127.5, 126.4, 124.0, 84.8, 79.7, 62.7, 31.2, 27.3, 0.7 ppm; EIMS (*m/z* (%)) M^+ not found, 524 $[M + Na]^+$ (60), 412 (50); HRMS (EI) calcd for $C_{19}H_{24}INO_3SSi$ $[M - Me]^+$ 486.0056, found 486.0057.

DoM and Desilylation of 3-Silyloxy Sultam 12: General Procedure 3. 7-Iodo-2-(2-phenylpropan-2-yl)-2,3-dihydrobenzo-[*d*]isothiazol-3-ol 1,1-Dioxide (13g). This compound was prepared according to General Procedure 1 with the following materials: **12** (0.67 g, 1.8 mmol), TMEDA (0.54 mL, 3.6 mmol), THF (18 mL), *s*-BuLi (2.6 mL, 1.38 M, 3.6 mmol), and I_2 (1.0 g, 3.9 mmol in 4.5 mL of THF). The crude material was dissolved in methanol (44 mL) and treated with K_2CO_3 (79 mg, 0.57 mmol). The reaction was followed to completion by TLC (10 min) before concentration in vacuo. Water (20 mL) was added and the mixture was transferred to an extraction funnel with EtOAc. The organic phase was separated, the aqueous layer was washed with EtOAc (2 × 20 mL), and the organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (18:7 hexanes: EtOAc) yielded **13g** (0.63 g, 83%) as a colorless solid: mp 111−112 °C; IR (KBr) υ_{max} 3452, 2980, 2948, 1278, 1189, 1131, 1067, 562 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91−7.90 (m, 1H), 7.56−7.54 (m, 2H), 7.42−7.40 (m, 1H), 7.37−7.35 (m, 2H), 7.30−7.25 (m, 2H), 5.49 (d, 1H, J = 10.3 Hz), 1.26 (s, 3H), 1.25 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 141.1, 138.5, 138.4, 134.0, 128.6, 127.7, 126.3, 124.7, 84.1, 79.1, 62.6, 29.0, 28.6 ppm; EIMS (*m/z* (%)) M^+ not found, 452 $[M + Na]^+$ (70), 412 (10), 334 (20), 237 (18), 119 (100); HRMS (EI) calcd for $C_{16}H_{16}INO_3S$ $[M + Na]^+$ 451.9638, found 451.9616.

7-Iodobenzo[*d*]isothiazol-3(2*H*)-one 1,1-Dioxide (14). Compound **13c** (102 mg, 0.204 mmol) was dissolved in MeOH (4 mL) and treated with K_2CO_3 (6.2 mg, 0.045 mmol). The reaction was followed to completion by TLC (15 min) before concentration in vacuo. Water (20 mL) was added and the mixture was transferred to an extraction funnel with EtOAc. The organic phase was separated, the aqueous layer was washed with EtOAc (2 × 20 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was redissolved in DMF (4 mL) under argon at room temperature and the resulting solution was stirred and treated with PDC (0.15 g, 0.41 mmol). After 24 h, water (20 mL) was added and the mixture was transferred to an extraction funnel with EtOAc. The organic phase was separated, the aqueous phase was extracted with EtOAc (2 × 10 mL), and the extracts were combined, washed with water (2 × 10 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (17:9 hexanes:EtOAc) yielded 7-iodo-2-(2-phenylpropan-2-yl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (83 mg, 95%) as a cream-colored solid: mp 148−149 °C; IR (KBr) υ_{max} 2987, 1707, 1336, 1285, 1202, 1163, 562 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.15 (dd, 1H, J = 0.6, 7.7 Hz), 7.83 (dd, 1H, J = 0.6, 7.7 Hz), 7.52−7.26 (m, 6H), 2.11 (s, 6H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.9, 145.0, 144.7, 141.2, 134.7, 129.2, 128.5, 127.2, 124.7, 124.2, 83.1, 64.9, 27.2 ppm; CIMS (*m/z* (%)) M^+ not found, 450 $[M + Na]^+$ (55), 332 (100), 119 (15); HRMS (CI) calcd for $C_{16}H_{14}INO_3S$ $[M + Na]^+$ 449.9627, found 449.9637. This product (51 mg, 0.165 mmol) was then dissolved in TFE (5 mL), heated at reflux for 22 h, cooled, and concentrated in vacuo and the resulting solid residue was triturated with diethyl ether to yield **14** (33 mg, 89%) as a light tan solid: sublimes at 255+ °C; IR (KBr) υ_{max} 3087, 2972, 2710, 1713, 1451, 1329, 1176, 588 cm^{-1}; ^1H NMR (200 MHz, DMSO) δ 8.30 (d, 1H, J = 7.4 Hz), 7.95 (d, 1H, J = 8.3 Hz), 7.58 (dd, 1H, J = 7.4, 8.3 Hz), 6.35 (br s, 1H) ppm; ^{13}C NMR (50 MHz, DMSO) δ 159.6, 144.6, 142.7, 135.5, 129.9, 124.2, 85.9 ppm; EIMS (*m/z* (%)) 309 $[M^+]$ (37), 246 (18), 202 (15), 119 (100); HRMS (EI) calcd for $C_7H_4INO_3S$ $[M^+]$ 308.8957, found 308.8969.

7-Iodobenzo[*d*]isothiazole 1,1-Dioxide (15). A solution of **13c** (52 mg, 0.1 mmol) in TFE (1.0 mL) was heated at reflux for 1.5 h and cooled. Concentration in vacuo and column chromatography (3:2 hexanes:EtOAc) yielded **15** (0.29 g, 94%) as a colorless solid: mp 161−162 °C; IR υ_{max} (KBr) 3072, 2924, 1634, 1334,

1170, 572 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 9.06 (s, 1H), 8.27 (d, 1H, J = 7.5 Hz), 8.01 (d, 1H, J = 7.7 Hz), 7.65−7.57 (m, 1H) ppm; ^{13}C NMR (50 MHz, acetone-d_6) δ 206.7, 164.4, 145.0, 143.7, 136.8, 134.2, 128.1, 87.8 ppm; EIMS (*m/z* (%)) 293 [M^+] (75), 245 (51), 202 (11), 176 (5), 166 (10), 149 (5), 138 (8), 127 (21), 118 (22), 107 (21), 102 (100); HRMS (EI) calcd for $C_7H_4NO_3S$ [M^+] 292.9008, found 292.8996.

7-Iodo-3-isopropoxy-2-(2-phenylpropan-2-yl)-2,3-dihydrobenzo[*d*]isothiazole 1,1-Dioxide (16). A solution of **13c** (51 mg, 0.11 mmol) in *i*-PrOH (1 mL) was heated at reflux for 48 h and cooled. Concentration in vacuo and column chromatography (3:2 hexanes:EtOAc) yielded **16** (36 mg, 75%) as a colorless solid: mp 91−93 °C; IR (KBr) υ_{max} 2991, 2950, 1298, 1189, 1144, 1016, 556 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96−7.95 (m, 1H), 7.53−7.50 (m, 2H), 7.47−7.45 (m, 1H), 7.36−7.33 (m, 2H), 7.30−7.25 (m, 2H), 5.79 (s, 1H), 3.78 (h, 1H, J = 6.1 Hz), 2.01 (s, 3H), 1.96 (s, 3H), 1.23 (d, 3H, J = 6.1 Hz), 0.75 (d, 3H, J = 6.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 141.1, 140.1, 137.3, 133.4, 128.3, 127.4, 126.3, 125.0, 84.7, 83.1, 67.0, 63.3, 30.8, 27.6, 23.9, 23.3 ppm; EIMS (*m/z* (%)) M^+ not found, 456 [M − Me]$^+$ (1), 414 (4), 352 (3), 295 (16), 293 (15), 245 (12), 119 (100); HRMS (EI) calcd for $C_{16}H_{15}INO_2S$ [M^+] 411.9868, found 411.9867.

Suzuki−Cross Coupling of 2-Iodo *N*-Cumyl Arylsulfonamides: General Procedure 4. A round-bottom flask fitted with a reflux condenser containing the appropriate iodide **5f**,**g**,**i** (1 mmol), boronic acid **17a**−**g** (1.1 − 2 mmol), and $Pd(PPh_3)_4$ (5 mmol %) was flushed thoroughly with argon before the addition of the following degassed solvent (5 mL) and base: Procedure 4A, DMF and K_3PO_4 (3 mmol) at 100 °C; Procedure 4B, THF and 2 M Na_2CO_3 (8−10 mmol) at 70 °C; Procedure 4C, THF and 0.35−2 M Cs_2CO_3 (2−8 mmol) at 70 °C; Procedure 4D, DME and 2 M Na_2CO_3 (10 mmol) at 90 °C. The reaction mixtures were heated under argon for 24 h, cooled, and processed as follows. Procedure A: The mixture was diluted with water (25 mL) and the whole was transferred to an extraction funnel with Et_2O, the organic phase was separated, and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL), washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Procedures 4B−D: After addition of water (10 mL), the whole was extracted with EtOAc (2 × 10 mL), and the organic extracts were combined, dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (hexanes:EtOAc).

2-Phenyl-*N*-(2-phenylpropan-2-yl)benzenesulfonamide (18a). This compound was prepared according to General Procedure 4A with the following materials: **5f** (0.500 g, 1.25 mmol), **17a** (0.300 g, 2.5 mmol), $Pd(PPh_3)_4$ (0.073 g, 0.063 mmol), K_3PO_4 (0.795 g, 3.75 mmol), and DMF (10 mL). Column chromatography (9:1 hexanes:EtOAc) yielded **18a** (0.334 g, 76%) as an oil: IR (neat) υ_{max} 3370, 2935, 1322, 1247, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, 1H, J = 1.1, 8.0 Hz), 7.59−7.18 (m, 13H), 3.94 (s, 1H), 1.40 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 142.6, 140.4, 139.9, 132.9, 132.4, 130.5, 130.3, 129.0, 128.8, 128.7, 128.4, 127.7, 125.9, 116.0, 59.4, 30.2 ppm; EIMS (*m/z* (%)) M^+ not found, 336 [M − Me]$^+$ (100), 153 (9), 120 (23), 119 (21); HRMS (EI) calcd for $C_{21}H_{21}NO_2S$ [M − Me]$^+$ 336.1072, found 336.1058.

2-(2,3-Dimethylphenyl)benzenesulfonamide (19a). This compound was prepared according to General Procedure 2 with the following materials: **18b** (190 mg, 0.50 mmol) and TFA (2 mL). Column chromatography (4:1 hexanes:EtOAc) yielded **19a** (120 mg, 92%) as colorless crystals: mp 176 °C (hexanes); IR (KBr) υ_{max} 3373, 3247, 1332, 1446, 1333, 1158 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 1H, J = 8.0 Hz), 7.62 (t, 1H J = 7.5 Hz), 7.51 (t, 1H J = 7.6 Hz), 7.27 (t, 2H, J = 7.6 Hz), 7.18 (t, 1H, J = 7.5 Hz), 7.10 (d, 1H, J = 7.5 Hz), 4.37 (s, 2H), 2.36 (s, 3H), 1.99 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6, 140.4, 138.2, 137.7, 135.9, 132.3, 131.9, 130.3, 127.7, 127.5, 127.2, 125.0, 20.5, 17.3 ppm; EIMS (*m/z* (%)) 261 [M^+] (1), 244 (93), 180 (41), 165 (100); HRMS (EI) calcd for $C_{14}H_{15}NO_2S$ [M^+] 261.0828, found 261.0824.

2-(*N*,*N*-Diethylcarboxamido)-6-phenyl-*N*-(2-phenylpropan-2-yl)benzenesulfonamide (20a). This compound was prepared according to General Procedure 1 with the following materials: **18a** (1.16 g, 3.30 mmol), TMEDA (1.1 mL, 7.27 mmol), *n*-BuLi (2.9 mL. 2.5 M, 7.27 mmol), THF (30 mL), and *N*,*N*-diethylcarbamoyl chloride (0.84 mL, 6.6 mmol), with the following changes: lithiation was carried out at 0 °C for 1 h. Column chromatography (4:1 hexanes:EtOAc) yielded **20a** (1.5 g, 99%) as a colorless solid: mp 109−110 °C (hexanes); IR (KBr) υ_{max} 3225, 2979, 1617, 1438, 1355, 1157, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, 1H, J = 7.6 Hz), 7.33−7.16 (m, 10H), 6.87 (br s, 1H), 5.70 (s, 1H), 3.74 (sx, 1H, J = 7.0 Hz), 3.45 (sx, 1H, J = 7.0 Hz), 3.18 (q, 2H, J = 7.1 Hz), 1.61 (s, 3H), 1.46 (s, 3H), 1.30 (t, 3H, J = 7.1 Hz), 1.13 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 146.1, 141.7, 139.5, 138.3, 136.8, 133.1, 130.9, 128.0, 127.7, 126.8, 126.7, 125.4, 59.6, 43.2, 39.1, 31.4, 29.0, 13.3, 12.0 ppm; EIMS (*m/z* (%)) M^+ not found, 435 [M − Me]$^+$ (4), 316 (82), 152 (61), 119 (100), 91 (95), 72 (65); HRMS (EI) calcd for $C_{16}H_{14}NO_2S$ [M^+] 450.1975, found 450.1977.

Synthesis of Substituted Saccharins: General Procedure 5. 7-Phenylbenzo[*d*]isothiazol-3(2*H*)-one 1,1-Dioxide (23a). This compound was prepared according to General Procedure 2 with the following materials: **20a** (190 mg, 0.42 mmol) and TFA (2 mL). Column chromatography (4:1−1:1 hexanes:EtOAc) afforded an oil that was dissolved in AcOH (10 mL) and the resulting solution was heated at reflux for 12 h. The cooled mixture was concentrated in vacuo to afford a solid residue that was dissolved in water (10 mL) and acidified (1M HCl) to pH 1, forming a precipitate that was collected by vacuum filtration yielding **23a** (98 mg, 90%) as colorless crystals: mp 222−223 °C (water); IR (KBr) υ_{max} 3082, 2954, 2712, 1714, 1456, 1340, 1161 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.03−7.95 (m, 3H), 7.73 (d, 2H, J = 7.67 Hz), 7.57−7.52 (m, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.2, 137.9, 137.4, 137.1, 136.0, 135.6, 129.7, 129.3, 129.2, 124.3 ppm; EIMS (*m/z* (%)) 259 [M]$^+$ (100). Anal. Calcd for $C_{13}H_9NO_3S$: C, 60.22; H, 3.50; N, 5.40; O, 18.51; S, 12.37. Found: C, 59.99; H, 3.48; N, 5.45; O, 18.98; S, 12.66.

2-(*N*,*N*-Diethylcarboxamido)-3-iodo-6-phenyl-*N*-(2-phenylpropan-2-yl)benzenesulfonamide (21a). This compound was prepared according to General Procedure 1 with the following materials: **20a** (1.20 g 2.65 mmol), TMEDA (0.88 mL, 5.83 mmol), *n*-BuLi (4.8 mL, 1.21 M, 5.83 mmol), THF (30 mL), and I_2 (1.35 g, 5.30 mmol, in 10 mL of THF), allowing only 1 h for metalation. Column chromatography (4:1 hexanes:EtOAc) and recrystallization yielded **21a** (800 mg, 53%) as colorless crystals: mp 91−92 °C (hexanes); IR (KBr) υ_{max} 3290, 2972, 1645, 1418, 1335, 1150, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 1H, J = 8.1 Hz), 7.29−7.25 (m, 9H), 6.75 (d, 2H, J = 8.1 Hz), 5.87 (s, 1H), 3.71 (sx, 1H, J = 7.1 Hz), 3.58 (sx, 1H, J = 7.1 Hz), 3.19 (h, 2H, J = 7.4 Hz), 1.59 (s, 3H), 1.45 (s, 3H), 1.36 (t, 3H, J = 7.1 Hz), 1.25 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 145.3, 141.8, 141.5, 140.1, 139.7, 139.0, 133.9, 130.6, 128.0, 127.8, 127.5, 127.1, 126.7, 125.5, 94.5, 59.5, 43.5, 39.3, 31.8, 28.5, 12.7, 11.9 ppm; EIMS (*m/z* (%)) M^+ not found, 561 [M − Me]$^+$ (4), 487 (5), 386 (7), 152 (25), 119 (100), 91 (50), 72 (95); HRMS (EI) calcd for $C_{26}H_{29}IN_2O_3S$ [M^+] 576.0955, found 576.0944.

2-(*N*,*N*-Diethylcarboxamido)-3,6-diphenyl-*N*-(2-phenylpropan-2-yl)benzenesulfonamide (22a). This compound was prepared according to General Procedure 4D with the following materials: **21a** (0.720 g, 1.25 mmol), **17a** (0.170 g, 1.38 mmol), $Pd(PPh_3)_4$ (0.070 g, 0.063 mmol), in DME (10 mL) and Na_2CO_3 (2 M, 5 mL). Column chromatography (4:1 hexanes:EtOAc) yielded **22a** (0.500 g, 76%) as colorless crystals: mp 175−176 °C (hexanes); IR (KBr) υ_{max} 3026, 2976, 1602, 1434, 1341, 1148, 981 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 2H, J = 7.1 Hz), 7.46−7.44

(m, 4H), 7.39 (d, 2H, J = 7.1 Hz), 7.31−7.29 (m, 4H), 7.19−7.12 (m, 4H), 6.81 (br s, 1H), 6.69 (br s, 1H), 3.57 (sx, 1H, J = 7.2 Hz), 3.08 (sx, 1H, J = 7.1 Hz), 2.98 (sx, 1H, J = 7.2 Hz), 2.70 (sx, 1H, J = 7.2 Hz), 1.64 (s, 3H), 1.55 (s, 3H), 0.82 (t, 6H, J = 7.4 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 145.7, 140.9, 140.1, 139.5, 138.9, 128.7, 134.3, 133.1, 132.5, 129.2, 128.3, 128.2, 127.9, 127.4, 126.6, 125.7, 59.5, 42.8, 38.3, 32.7, 28.5, 12.3, 11.4 ppm; EIMS (*m/z* (%)) M^+ not found, 511 $[M - Me]^+$ (3), 438 (9), 392 (12), 336 (20), 119 (100), 91 (83), 72 (60); HRMS (EI) calcd for $C_{32}H_{34}N_2O_3S$ $[M^+]$ 526.2277, found 526.2290.

4,7-Diphenylbenzo[*d*]isothiazol-3(2*H*)-one 1,1-Dioxide (23e). This compound was prepared according to General Procedure 5 with the following materials: **22a** (200 mg, 0.379 mmol) and TFA (2 mL). Following column chromatography (4:1 hexanes:EtOAc) and treatment with AcOH (10 mL), the resulting precipitate was collected by filtration to yield **23e** (100 mg, 79%) as colorless crystals: mp 282−283 °C (water); IR (KBr) υ_{max} 2953, 2710, 1725, 1476, 1335, 1150 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, 1H, J = 7.9 Hz), 7.79 (d, 1H, J = 7.9 Hz), 7.74 (d, 2H, J = 6.9 Hz), 7.58−7.53 (m, 5H), 7.46 (d, 3H, J = 3.0 Hz) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.7, 141.3, 138.8, 137.5, 137.3, 137.0, 136.7, 135.9, 130.0, 129.6, 129.5, 129.2, 128.7, 128.2, 125.2 ppm; EIMS (*m/z* (%)) 335 $[M^+]$ (100), 226 (71), 113 (50), 69 (100); HRMS (EI) calcd for $C_{19}H_{13}NO_3S$ $[M^+]$ 335.0606, found 335.0616.

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Supporting Information Available: Experimental procedures and characterization data for the synthesis of substituted *N*-cumylsulfonamides **5b**−**i**, **21b**, **22b**, sultam **6**, secondary *N*-cumylsulfonamide **9**, *N*-ethylsulfonamide **11**, substituted *N*-cumyl sultams **13a**,**b**,**d**−**f**, *N*-cumyl biarylsulfonamides **18b**−**k**, primary biarylsulfonamides **19b**−**e**, and substituted saccharins **23b**−**d**,**f**, and ^{1}H NMR and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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