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Directed Ortho Metalation Methodology. The *N*,*N*-Dialkyl Aryl *O*-Sulfamate as a New Directed Metalation Group and Cross-Coupling Partner for Grignard Reagents

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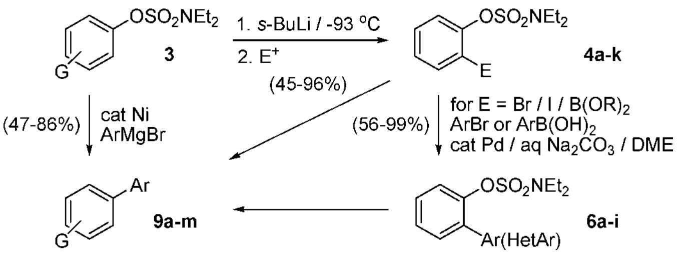
ABSTRACT



The ortho metalation (RLi/THF/–93 °C) of 3 followed by quench with a variety of electrophiles constitutes a new general route to substituted aryl *O*-sulfamates 4a–k. The Kumada–Corriu cross-coupling of *O*-sulfamates 4e, 4n–s, and 6a with Grignard reagents gives biaryls 9a–m, and the use of 2-halo and boron derivatives 4h, 4i, and 4k for Suzuki–Miyaura cross-coupling and generation of benzynes leads to naphthols 7a and 7b. A relative metalation ranking of the OSONEt$_2$ is reported.

The conjunction of the directed ortho metalation (DoM) strategy (Figure 1, **1**)[1,2] with various transition metal-catalyzed cross-coupling regimens[3] has established a fountainhead of reliable methodology for the regioselective construction of biaryls in a multitude of aryl−aryl and aryl−heteroaryl bond-forming combinations.[4] In the context of the subsequent manipulation of directed metalation groups (DMGs), always an important part of synthetic planning, the powerful *O*-carbamate DMG[5] and, recently, the sulfonamide

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(1) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(2) Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002; p 330.

(3) For recent comprehensive reviews, see the dedicated special issue: Tamao, K.; Hiyama, T.; Negishi, E.-i. (Eds.) *J. Organomet. Chem.* **2002**, *653*. Diederich, F., Stang, P. J., Eds. *Metal-catalyzed Cross-coupling Reactions*; Wiley-VCH: Weinheim, 1998. Stille coupling: Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551. Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704. Negishi coupling: King, A. O.; Negishi, E.-i.; Villani, F. J.; Silveira, A. *J. Org. Chem.* **1978**, *43*, 358. Klement, I.; Rottlander, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201. Hiyama coupling: Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, *845*. Denmark, S. E.; Sweis, T. F. *Acc. Chem. Res.* **2002**, *35*, 835. Suzuki−Miyaura coupling: Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 867. Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. Corriu−Kumada−Tamao coupling: Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144. For a recent copper-catalyzed coupling of siloxanes, see: Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600. Copper-catalyzed coupling of boronic acids: Lam, P. Y. S.; Bonne, D.; Vincent, G.; Clark, C. G.; Combs, A. P. *Tetrahedron Lett.* **2003**, *44*, 691 and refs cited therein. Iron-catalyzed coupling: Fürstner, A.; Martin, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955 and references cited therein.

(4) Anctil, E. J. G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150. 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; p 761.

(5) Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066. A useful element of the *O*-carbamate is its proclivity for anionic ortho Fries rearrangement exposing a phenol that, upon triflation and Ni-catalyzed hydride reduction, also achieves its removal

10.1021/ol050393c CCC: $30.25

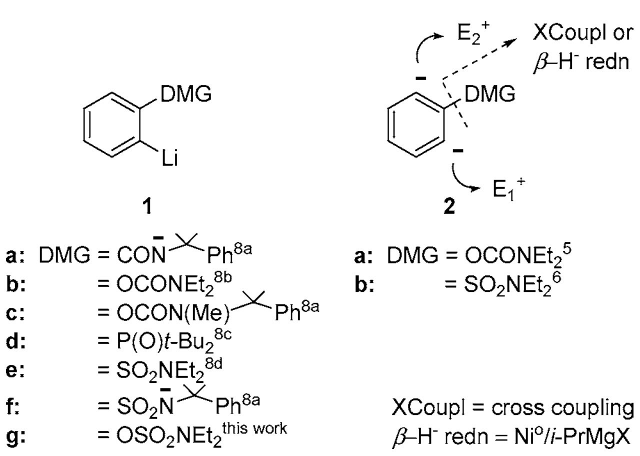
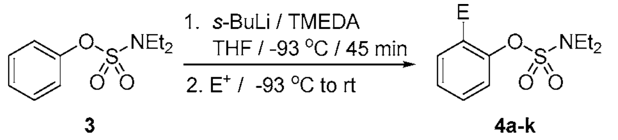


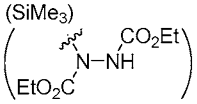
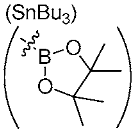
Figure 1.

DMG[6] have shown the additional features of latency and cross-coupling capability (**2**), hence enhancing the synthetic utility especially in the context of synthesis of meta-substituted aromatics. Herein we report preliminary results that demonstrate that the *O*-sulfamate (**3**),[7] derived by the union of $OCONR_2$[8b] and SO_2NR_2[8d] groups, is a new DMG and cross-coupling partner in the Kumada−Corriu reaction and that the 2-halo and boron derivatives **4h**, **4i**, and **4k** undergo Suzuki−Miyaura cross-coupling and provide a new entry to the benzyne species. In sum, the reported work provides new methods of general utility in synthetic aromatic chemistry.

At the outset, the similarity of the *O*-sulfamate to OTs,[9] OMs,[10] and especially OTf[11] groups raised concerns that it would suffer, perhaps with similar propensity, ortho anion-induced benzyne formation,[12] an apprehension that was verified at the −78 °C temperatures commonly used for DoM chemistry. However, at −93 °C (internal temperature by thermocouple measurement), the simply prepared[13] prototype *O*-sulfamate **3** underwent smooth ortho metalation to the intermediate lithiated species, which, upon quench with a variety of electrophiles, provided products **4** in modest to excellent yields (Table 1).[14] Thus, introduction of standard (entries 1 and 3) and DMG (entry 2) carbon, sulfur (entry 4), silicon (entry 5), and nitrogen (entry 6) electrophiles proceeds unexceptionally; furthermore, halogen (entries 7−9), tin (entry 10), and boron (entry 11) electrophiles may be introduced, thus inviting a study of cross-coupling chemistry. In the event, the 2-iodo *O*-sulfamate **4i** and, in one case, the corresponding bromo derivative **4h** (entry 7), when subjected to standard Suzuki−Miyaura cross-coupling conditions with a selection of arylboronic acids **5**, afforded

Table 1. Metalation and Electrophile Quench of Phenyl *O*-Sulfamate **3**[a]



entry	E^+	product (E)	yield (%)
1	DMF	**4a** (CHO)	63
2	$ClCONEt_2$	**4b** ($CONEt_2$)	70
3	PhCHO	**4c** (CH(OH)Ph)	85
4	MeSSMe	**4d** (SMe)	88
5	Me_3SiCl	**4e** ($SiMe_3$)	96
6	DEAD	**4f** 	53
7	Cl_3CCCl_3	**4g** (Cl)	45
8	$Br_2CHCHBr_2$	**4h** (Br)	56
9	I_2	**4i** (I)	78
10	Bu_3SnCl	**4j** ($SnBu_3$)	91
11	(1) $B(O^iPr)_3$, (2) pinacol	**4k** 	87

[a] Typical procedure: (1) 1.1 equiv of *s*-BuLi/TMEDA/THF/−93 °C/45 min/0.2−0.5 M; (2) E^+/−93 °C to room temperature.

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with retention of a new amide DMG for further DoM chemistry; see: Cai, X.; Brown, S.; Hodson, P.; Snieckus, V. *Can. J. Chem.* **2004**, *82*, 195 and refs cited therein. For the power and versatility of the *O*-carbamate DMG in synthesis, see: Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.

(6) Milburn, R. R.; Snieckus, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 892. Milburn, R. R.; Snieckus, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 888.

(7) Review: Benson, G. A.; Spillane, W. J. In *The Chemistry of Sulphonic Acids, Esters, and their Derivatives*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991; p 987 ff. *O*-Sulfamates are of interest in medicinal chemistry; see: Spillane, W. J.; McGrath, P.; Brack, C.; O'Byrne, A. B. *J. Org. Chem.* **2001**, *66*, 6313 and refs cited therein. For use of *O*-sulfamates in Ru-catalyzed C−H-activated processes, see: Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823 and refs cited therein. For thia-Fries rearrangement of *O*-sulfamates, see: Benson, G. A.; Maughan, P. J.; Shelly, D. P.; Spillane, W. J. *Tetrahedron Lett.* **2001**, *42*, 8729 and refs cited therein.

(8) (a) Metallinos, C.; Nerdinger, S.; Snieckus, V. *Org. Lett.* **1999**, *1*, 1183. (b) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935. (c) Gray, M.; Chapell, B. J.; Felding, J.; Taylor, N. J.; Snieckus, V. *Synlett* **1998**, 422. (d) MacNeil, S. L.; Familoni, O. B.; Snieckus, V. *J. Org. Chem.* **2001**, *66*, 3662 and refs cited therein.

(9) DoM chemistry of this function has, to the best of our knowledge, not been achieved. For cross-coupling chemistry, see: Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058 (Suzuki−Miyaura). Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704 (Kumada−Corriu).

(10) For Suzuki−Miyaura cross-coupling, see: Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447.

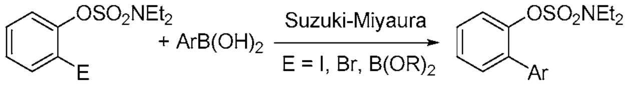
(11) For Negishi coupling, see: Quesnelle, C. A.; Familoni, O. B.; Snieckus, V. *Synlett* **1994**, 349.

(12) Benzyne generation may be achieved by elimination from 1,2-dihalides; see: Wittig, G.; Benz, E. *Chem. Ber.* **1959**, *92*, 1999. Franzen, V.; Joschek, H. I.; Mertz, C. *J. Liebigs Ann. Chem.* **1962**, *654*, 82. Seyferth, D.; Menzel, H. H. A. *J. Org. Chem.* **1965**, *30*, 649. Brewer, J. P. N.; Heaney, H. *Tetrahedron Lett.* **1965**, 4709. By DMG-induced deprotonation−halide elimination, see: Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178. Clark, R. D.; Caroon, J. M. *J. Org. Chem.* **1982**, *47*, 2804. By fluoride-mediated elimination from *ortho*-TMS aryl halides and triflates, see: Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211. Tsukazaki, M.; Snieckus, V. *Heterocycles* **1992**, *33*, 533. Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta* **2002**, *85*, 3589.

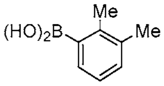
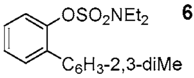
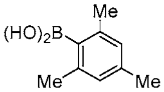
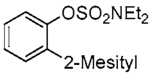
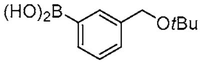
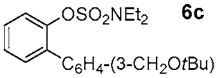
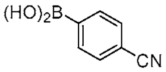
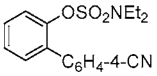
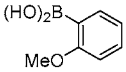
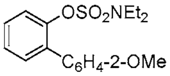
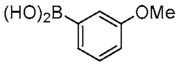
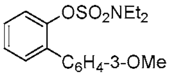
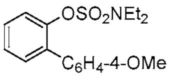
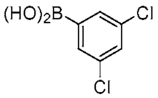
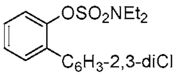
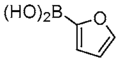
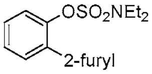
(13) Gupta, S. K. *Synthesis* **1977**, 39.

(14) In an attempt to trap the thermodynamically generated anion, treatment of **3** under Martin conditions (**1g**: LiTMP/TMSCl = 1:2.1:10) (Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155) led to SM (35%), **4e** (41%), and 2,2,6,6-tetramethyl-1-(2-(trimethylsilyl)phenyl)-piperidine (19%) by GC analysis.

Table 2. Suzuki−Miyaura Cross-Coupling 2-Bromo-, 2-Iodo-, and 2-Pinacolboronate *O*-Phenylsulfamate **4h**, **4i**, and **4k**[a]



4h, i, k **5** **6a-i**

entry	E	$ArB(OH)_2$ (**5**)	product		yield (%)
1	I (**4i**)		 C_6H_3-2,3-diMe	**6a**	85
2[b]	I (**4i**)		 2-Mesityl	**6b**	56
3	I (**4i**)		 C_6H_4-(3-CH_2O*t*Bu)	**6c**	99
4	I (**4i**)		 C_6H_4-4-CN	**6d**	93
5	I (**4i**)		 C_6H_4-2-OMe	**6e**	85
6	I (**4i**)		 C_6H_4-3-OMe	**6f**	92
7	Br (**4h**)	4-$MeOC_6H_4B(OH)_2$	 C_6H_4-4-OMe	**6g**	85
8	$B(OR)_2$ (**4k**)	4-Bromoanisole			93
9	I (**4i**)		 C_6H_3-2,3-diCl	**6h**	91
10[b]	I (**4i**)		 2-furyl	**6i**	76

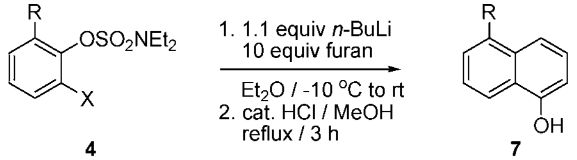
[a] Typical procedure: 1 equiv of ArX/5 mol % $Pd(PPh_3)_4$/DME/2 M Na_2CO_3/80 °C/16 h. [b] Performed with 2 equiv of ArX/10 mol % $Pd(PPh_3)_4$/40 h.

products **6** in excellent yields (Table 2). One inverted partner combination was tested (entry 8) to demonstrate that comparable yields may be obtained from reactions of either combination of cross-coupling partners.

Reaction block experiments defined conditions for benzyne trapping of **4h** using furan as the diene to give 7-oxabenzonorbornadiene, which was converted to **7a** in 21% yield (Scheme 1). Subjection of the *ortho*-bromo *O*-sulfamates **4l** and **4m** to metal−halogen exchange at −10 °C in the presence of furan followed by catalytic HCl treatment afforded naphthols **7a** (concurrent protodesilylation) and **7b** in 50 and 31% yields, respectively. Improvement of yields was achieved by adapting the Knochel protocol for Grignard generation[15] on **4i**, which, after furan trap and acid hydrolysis, furnished **7a** in 70% yield.[16]

Encouraged by the results of *O*-carbamate[5] and related phenol-derived cross-coupling partners,[9−11] we screened a number of nickel catalysts[17] on **3** using *p*-tolylmagnesium bromide as a standard Grignard partner (Table 3). While using nonliganded (entries 1 and 2) and phosphine mono- (entry 3) and bidentate (entry 4) Ni catalysis already provided reasonable yields of product **8**, use of Cp-containing catalysts (entries 5−9) showed considerable enhancement in yields, with the air-stable, conveniently handled NiClCpIMes performing as a superb catalyst at low loading in ether at room temperature to afford **8** in quantitative yield.[18]

Scheme 1

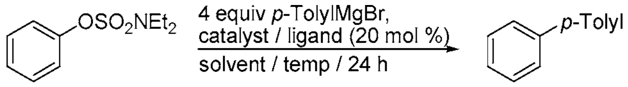


4 **7**

4	X	R	**7**	R	
h	Br	H	**a**	H	(21%)
l	Br	TMS	**a**	H	(50%)
m	Br	OMe	**b**	OMe	(31%)
i	I	H	**a**	H	(70%)[a]

[a] Knochel protocol: (1) 1.1 equiv of *i*-PrMgCl/Et_2O/−78 °C/30 min; (2) 10 equiv of furan/−78 °C to rt; (3) cat. HCl/MeOH/reflux/3 h.

Table 3. Optimization of Conditions for the Ni-Catalyzed Phenyl *O*-Sulfamate **3**-*p*-Tolyl Grignard Cross-Coupling Reaction



3 **8**

entry	catalyst/ligand	solvent	temp (°C)	yield (%)[a]
1	$Ni(acac)_2$	PhMe	120	29
2	$NiCl_2$	PhMe	120	72
3	$NiCl_2$/P(*t*-Bu)$_3$	PhMe	120	63
4	$NiCl_2$/dppf	PhMe	120	74
5	$NiClCpPPh_3$	Et_2O	40	83
6	$NiClCpPPh_3$	PhMe	120	91
7	NiClCpIMes	THF	40	83
8	NiClCpIMes	PhMe	40	85
9	**NiClCpIMes**	**Et_2O**	**40**	>**99**

[a] Determined by GC (undecane as internal standard).

Using this optimized set of conditions, cross-coupling reactions of selected aryl *O*-sulfamate−aryl Grignard reagent

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[15] Sapountzis, I.; Lin, W.; Fischer, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4364.

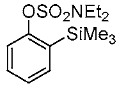
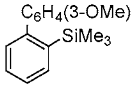
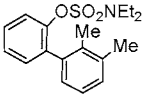
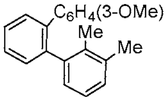
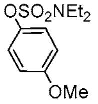
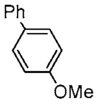
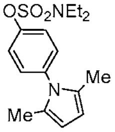
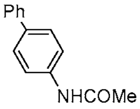
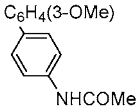
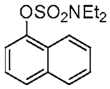
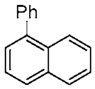
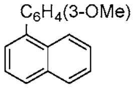
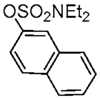
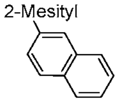
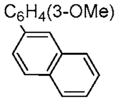
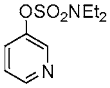
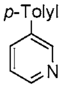
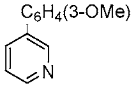
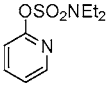
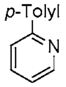
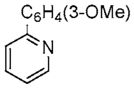
[16] Generalization of this result is being pursued.

[17] $Pd(PPh_3)_4$, (IPr)Pd(allyl)Cl (Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173), and $Fe(acac)_3$ (Fürstner, A.; Leitner, A.; Menendez, M. M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856) catalysis was ineffective and led to recovery of starting material.

[18] High activity of NiClCpIMes may be attributed to the presence of a low-valent electron-rich metal center owing to a strongly Lewis basic, electron σ-donating carbene ligand whose steric nature accelerates the reductive elimination step, see: Bohm, V. P. W.; Gstottmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3387. Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889.

Table 4. Ni-Catalyzed Aryl Cross-Coupling of Aryl *O*-Sulfamates with Aryl Grignard Reagents[a]

$$\underset{\textbf{4e, l-s, 6a}}{\mathrm{ArOSO_2NEt_2}} + \mathrm{Ar'MgBr} \xrightarrow[\mathrm{Et_2O}]{\mathrm{[NiClCpIMes]}} \underset{\textbf{9a-m}}{\mathrm{Ar{-}Ar'}}$$

entry	4, 6		Ar'MgBr	product		temp time	yield (%)
1		**4e**	$BrMgC_6H_4$ (3-OMe) (2.5 equiv)		**9a**	40°C 12 h	76
2		**6a**	$BrMgC_6H_4$ (3-OMe) (2.5 equiv)		**9b**	40°C 30 h	64
3		**4n**	BrMgPh (2.5 equiv)		**9c**	40°C 19h	47
4[b]		**4o**	BrMgPh (2.0 equiv)		**9d**	rt 1 h	50
5[b]		**4o**	$BrMgC_6H_4$ (3-OMe) (2.0 equiv)		**9e**	rt 3 h	46
6		**4p**	BrMgPh (1.2 equiv)		**9f**	0 °C 10 min	84
7		**4p**	$BrMgC_6H_4$ (3-OMe) (2.0 equiv)		**9g**	rt 1 h	79
8		**4q**	2-Mesityl MgBr (2.5 equiv)		**9h**	40 °C 18 h	69
9		**4q**	$BrMgC_6H_4$ (3-OMe) (2.5 equiv)		**9i**	rt 1 h	86
10		**4r**	*p*-TolylMgBr (2.5 equiv)		**9j**	rt 18 h	71
11		**4r**	$BrMgC_6H_4$ (3-OMe) (2.5 equiv)		**9k**	rt 18 h	85
12		**4s**	*p*-TolylMgBr (2.0 equiv)		**9l**	rt 8 h	82
13		**4s**	$BrMgC_6H_4$ (3-OMe) (2.0 equiv)		**9m**	rt 4 h	73

[a] Typical procedure: 1.2−2.5 equiv of Ar′MgBr/1−2.5 mol % NiClCpIMes/Et_2O/0−40 °C/0.1−19 h. [b] Deprotection/acylation: 10 equiv of hydroxylamine HCl/2 equiv of NEt_2/2:1 EtOH−H_2O/90 °C/24 h, then 1.2 equiv of acetic anhydride/2 equiv of NEt_3/CH_2Cl_2/rt/1 h.

combinations were carried out to afford biaryl products **9a**−**m** in synthetically useful yields (Table 4). Aside from simple biaryls (entries 1, 3, and 5−8) and a tertaryl (completing a metal-tuned coupling sequence, entry 2), N-protected anilines (entries 3 and 4) and azabiaryls (entries 9−12) were unexceptionally obtained.[19,20] To obtain preliminary evidence for the hierarchal position of the *O*-sulfamate vis-á-vis other DMGs,[2] inter- and intramolecular competition experiments were carried out (Figure 2). Thus, treatment of 4-$CONEt_2$ phenyl *O*-sulfamate (**4t**) under the standard conditions for 10 min followed by CD_3OD quench led to the formation of **10a** and **10b** in a 17:1 ratio based on d_1-NMR. Using the same experimental protocol, a 1:1 mixture of *N*,*N*-diethyl phenyl *O*-carbamate and **3** afforded deuterated **11** and **12** in a 23:1 ratio. Thus, the *O*-sulfamate is a relatively poor DMG compared to the tertiary amide and the tertiary *O*-carbamate, which are near the top of the qualitatively assessed ranking list.[2]

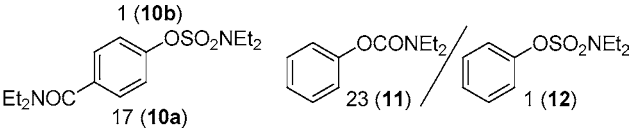


Figure 2. Ratios of D-incorporation products from intra- and intermolecular DoM competition experiments.

In conclusion, we have shown that the *O*-sulfamate is a new, albeit moderate strength, DMG. *ortho*-Halo and boron products **4h**, **4i**, and **4k** participate in Suzuki−Miyaura cross-coupling, and, perhaps more significantly, the *O*-sulfamates themselves undergo Kumada−Corriu coupling, both reactions leading to functionalized and potentially bioactive biaryls (Tables 2 and 4). The new reactions extend DoM concepts and protocols for application in synthetic endeavors.

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Supporting Information Available: Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Attempts to de-O-sulfamoylate **4n** in a manner analogous to that used for arylsulfonamides[6] led only to the formation of *p*-isopropylanisole in low yield.

(20) To demonstrate a further DoM−cross-coupling link of potential synthetic utility, the prototype phenyl *O*-sulfamate **3** was subjected to cross-coupling with *p*-tolylboronic acid under Suzuki conditions to afford **8** albeit in modest 64% yields (GC) using 20 mol % Ni$(acac)_2$/dppp and 2 equiv of *p*-TolylB$(OH)_2$/K_3PO_4 in PhMe at 90 °C for 24 h.