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The Diastereoselective Alkylation of Arenesulfenate Anions Using Homochiral Electrophiles

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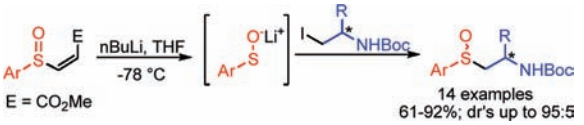
ABSTRACT



A series of Boc-protected β-amino sulfoxides were prepared by the reaction of arenesulfenate anions with chiral Boc-protected β-amino iodides. The stereoselective substitution reaction is believed to arise through precoordination of the sulfenate counterion with the nitrogen lone pair of the electrophile.

Sulfenic acid anions (sulfenates), which are defined by the structure C−S−O^-M^+,[1] have emerged as useful reactive nucleophiles in organic chemistry. Their prochiral nature makes them potential sources of asymmetric sulfur compounds upon functionalization. Sulfenates hold significant unexplored reactivity, and their use for sulfoxide synthesis is counter to the paradigms of sulfide oxidation and nucleophilic attack at sulfur for the formation of asymmetric sulfinyl containing compounds.[2,3]

A number of recent studies have confirmed that S-functionalization of sulfenates can occur with enantio- or diastereoselectivity. For instance, Madec, Poli and coworkers have demonstrated enantioselective sulfoxide formation through transition metal catalyzed C−S bond formation.[1b,4] The Perrio group has established examples of diastereoselective alkylation with cyclophane[5] or carbon stereogenicity[6] in the sulfenate structure. A conceptually new protocol calls on chiral phase transfer catalysis for access to stereoenriched sulfoxides.[7] Tanaka and co-workers demonstrated the value of proximal oxygen atoms within a chiral sulfenate for diastereoselective alkylation reactions.[8] The Schwan group has recently published work concerning diastereoselective alkylations of a protected cysteinesulfenate,[9] which provides a complementary protocol to cysteinesulfenic acid addition chemistry.[10]

To our knowledge there has only been one report of the use of a chiral *electrophile* for the formation of asymmetric sulfinyl containing compounds.[11] Using (*R*)- and (*S*)-configured sulfonium salts as alkylating agents, methyl and ethyl sulfoxides were obtained in yields up to 44% and with modest enantioselectivity (ee = 24%), through chemistry proposed to involve a sulfurane intermediate (Scheme 1). Given the increased recognition of sulfenates as a source of

(1) (a) O'Donnell, J. S.; Schwan, A. L. *J. Sulfur Chem.* **2004**, *25*, 183. (b) Maitro, G.; Prestat, G.; Madec, D.; Poli, G. *Tetrahedron: Asymmetry* **2010**, *21*, 1075.

(2) O'Mahony, G. E.; Kelly, P.; Lawrence, S. E.; Maguire, A. R. *Arkivoc* **2011**, No. (i), 1.

(3) Stingl, K. A.; Tsogoeva, S. B. *Tetrahedron: Asymmetry* **2010**, *21*, 1055.

(4) (a) Maitro, G.; Prestat, G.; Madec, D.; Poli, G. *J. Org. Chem.* **2006**, *71*, 7449. (b) Maitro, G.; Vogel, S.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2006**, *8*, 5951. (c) Maitro, G.; Vogel, S.; Sadaoui, M.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2007**, *9*, 5493. (d) Bernoud, E.; Le, D. G.; Bantreil, X.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2010**, *12*, 320.

(5) Lohier, J.-F.; Foucoin, F.; Jaffres, P.-A.; Garcia, J. I.; Sopkova-de Oliveira Santos, J.; Perrio, S.; Metzner, P. *Org. Lett.* **2008**, *10*, 1271.

(6) Sandrinelli, F.; Perrio, S.; Averbuch-Pouchot, M.-T. *Org. Lett.* **2002**, *4*, 3619.

(7) Gelat, F.; Jayashankaran, J.; Lohier, J.-F.; Gaumont, A.-C.; Perrio, S. *Org. Lett.* **2011**, *13*, 3170.

(8) Maezaki, N.; Yagi, S.; Ohsawa, S.; Ohishi, H.; Tanaka, T. *Tetrahedron* **2003**, *59*, 9895.

(9) Schwan, A. L.; Verdu, M. J.; Singh, S. P.; O'Donnell, J. S.; Ahmadi, A. N. *J. Org. Chem.* **2009**, *74*, 6851.

(10) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P. *Curr. Org. Chem.* **2007**, *11*, 1034.

(11) Kobayashi, M.; Manabe, K.; Umemura, K.; Matsuyama, H. *Sulfur Lett.* **1987**, *6*, 19.

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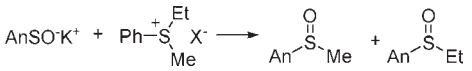
Scheme 1. A Past Attempt of Stereoselective Alkylation of a Sulfenate Using a Chiral Electrophile (An = 1-Anthraquinoyl; X^- = d-Camphorsulfonate)



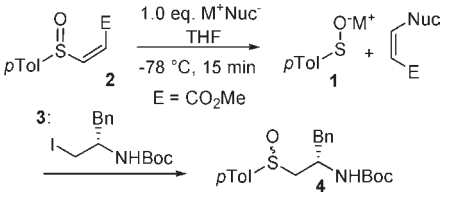
asymmetric sulfinyl containing compounds,[6,9,5,1b,8,12] we now report the use of homochiral iodides as electrophiles to induce chirality at sulfur. The value of chiral sulfoxides in organic synthesis is well documented.[13]

Our group has previously established that the lithium counterion is important in the diastereoselectivity during cysteinesulfenate benzylation. This is proposed to occur by internal coordination to the amino acid nitrogen,[9] in accord with a related system of the Perrio group.[6] This concept suggested that a bimolecular precoordination may be important to achieving diastereoselective alkylations. As such, the first foray into this chemistry involved the use of nitrogen and carboxyl protected serinyl iodides. Unfortunately, only dehydroalanines were obtained when a series of iodides was reacted with lithium *p*-toluenesulfenate (**1-Li**), the latter generated from methyl (*Z*)-2-*p*-tolylsulfinylacrylate (**2**).[14] Attribution of this reactivity mode to the high acidity of the α-hydrogen of protected iodides and hence their proclivity for elimination led us to a different set of electrophiles. Specifically, iodides derived from common amino acids by way of carboxyl reduction, nitrogen protection, and hydroxyl-to-iodide conversion[15] were explored.

Focusing on the use of Boc protection,[16] some of our preliminary experiments using nitrogen protected (*S*)-2-amino-3-phenylpropyl iodide (**3**), derived from L-phenylalanine, and *p*-toluenesulfenate (**1**) are indicated in Table 1. The *β*-sulfinyl acrylate ester was dissolved in THF, chilled to −78 °C, treated with a nucleophile, and stirred for 15 min to allow sulfenate generation. The Boc protected amino iodide (**3**) in THF was then added at −78 °C to the sulfenate solution. The reaction mixture was stirred for 3 h at −78 °C and then allowed to slowly warm to room temperature. Boc-protected amino sulfoxide **4** was isolated and subjected to flash chromatography to obtain a chemical yield. The diastereomeric ratios were determined using an HPLC equipped with a Daicel OJ-H column.

Various modes of sulfenate generation and counterion identity were explored.[17] The data in Table 1 reveal the

Table 1. Preliminary Alkylation Attempts of *p*-Toluenesulfenate (**1**) with Electrophile **3**



M^+Nuc^-	solvent	dr	yield (%)
$Li^+ {}^-OMe$	THF	90:10	52
$Na^+ {}^-OMe$	THF	78:22	88
$K^+ {}^-OMe$	THF	58:42	57
$Li^+ {}^-SC_6H_{11}$	THF	91:9	46
$Na^+ {}^-SC_6H_{11}$	THF	70:30	83
$Li^+ {}^-OMe$	THF/12-c-4[a]	78:22	61
$Li^+ {}^-Bu$	THF	91:9	87
$Li^+ {}^-Bu$	THF/MeOH[b]	68:32	61

[a] 4 equiv of 12-crown-4 were added to the alkylation mixture. [b] 0.2 equiv of MeOH was introduced after sulfenate formation.

importance of the lithium counterion for high dr, but sodium typically provided the superior chemical yield. The introduction of 12-crown-4 and the consequent attenuated dr are suggestive of an important role for the lithium counterion in the stereochemical outcome. Finally, the use of BuLi to release *p*-toluenesulfenate from the sulfinyl acrylate provided the best de with a surprisingly high yield. The introduction of MeOH after sulfenate formation reduced the dr and yield significantly. The interpretation is not that BuLi is necessarily a superior reagent for the generation of **1-Li**, but rather that it ensures the absence of hydroxylic species which may be attenuating diastereoselectivity and yield.

It has long been recognized that more reactive electrophiles, such as benzyl bromides and methyl iodides, alkylate sulfenates most efficiently.[1a] To achieve high yields of sulfoxide with less reactive materials, an excess of an electrophile is often required. Although we adopted only a 2-fold excess of a chiral electrophile, the generally high yields of alkylation came as a surprise, especially since iodide **3** exhibits significant steric hindrance on the carbon *β* to the iodide. As such we performed a competition experiment with equal molar amounts of **3** and $PhCH_2Br$. With **1-Li** as the limiting reagent to mimic pseudo-first-order conditions, benzylation was observed as the only alkylation event. However, in a similar competition using ^{n}Bu-I vs **3**, alkylation with **3** proved ca. four times faster, even though a steric bias should prefer butylation. Some mode of precoordination of the heteroatom(s) of **3** is presumably an accelerating influence in favor in its alkylation, and this is expected to be a key contributor to the observed stereoselectivity (*vide infra*). Moreover, the result is also evocative in that electrophiles with heteroatoms proximal to the carbon leaving group bond may accelerate sulfenate reactivity, heretofore an unobserved result in sulfenate chemistry.[18]

(12) Caupene, C.; Boudou, C.; Perrio, S.; Metzner, P. *J. Org. Chem.* **2005**, *70*, 2812.

(13) (a) Carmen, C. M.; Hernandez-Torres, G.; Ribagorda, M.; Urbano, A. *Chem. Commun.* **2009**, 6129. (b) Wojaczynska, E.; Wojaczynski, J. *Chem. Rev.* **2010**, *110*, 4303.

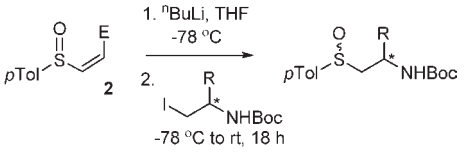
(14) O'Donnell, J. S. PhD Thesis. University of Guelph, 2005.

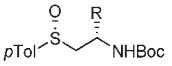
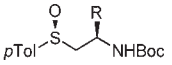
(15) (a) Caputo, R.; Cassano, E.; Longobardo, L.; Palumbo, G. *Tetrahedron Lett.* **1995**, *36*, 167. (b) Mosa, F.; Thirsk, C.; Vaultier, M.; Maw, G.; Whiting, A. *Org. Synth.* **2008**, *85*, 219.

(16) Boc was selected due to its demonstrated success with cysteinyl sulfoxides. See ref 9.

(17) The chemistry employed does not tolerate a wide selection of solvents, and variations within the narrow realm of options were of no benefit.

Table 2. Reactions of Sulfenate **1-Li** with Various Chiral Electrophiles



	R	product[a]		dr[b]	yield (%)
1	Bn	(R_S,S_C)	**4**	91:9	87
2	CH_3		**5**	87:13	81
3	*i*-Pr		**6**	90:10	71
4	***i*-Bu**		**7**	91:9	92
5	Ph	(S_S,R_C)	**8**	73:27	79
6	Bn		***ent*-4**	92:8	84
7	Et		**9**	94:6	81

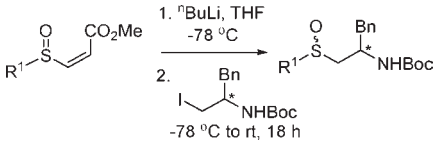
[a] Product drawn and numbered is major isomer obtained. [b] Major isomer listed first.

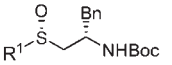
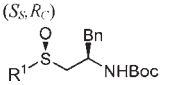
Given the optimized conditions for the alkylation, attention was turned to changing the amino acid R group. Electrophiles of both configurations were employed and yields ranged from 71% to 92%, with dr's consistently approaching or exceeding 9:1, with the exception of R = Ph (ca. 3:1, Table 2).

Further evaluation of the scope of diastereomeric alkylation focused on the identity of the sulfenate. Benzene- and 2-naphthalenesulfenates delivered comparable alkylation chemistry with electrophile **3**. The lower yield of **13** may be due to chemoselectivity problems wherein the *n*BuLi reacts with the bromine of the 2-bromophenyl group. To improve the yield, we reverted to LiOMe for more directed sulfenate release and obtained 71% yield with a reduced 83:17 dr. Alkanesulfenates, exemplified by entry 6 in Table 3, did not get alkylated by iodide **3**.[19] In all cases presented in Tables 2 and 3, the major diastereomer could be obtained in pure form after one or two recrystallizations. The absolute configurations of the products were established by comparison to literature optical rotation values.[20,21]

To account for the observed stereochemistry, one could invoke a lithium to nitrogen precomplex as indicated

Table 3. Reactions of Various Sulfenates with Chiral Amino Iodides **3** and ***ent*-3**



	R^1	product[a]		dr[b]	yield
1	Ph	(R_S,S_C)	**10**	91:9	71
2	*o*-$CH_3C_4H_6$		**11**	87:13	81
3	2-naphthyl		**12**	88:12	91
4	*o*-BrC_4H_6		**13**	90:10	64
5	*o*-BrC_4H_6[c]		**13**	83:17	71
6	*n*-hexyl[d]		**14**	--	0
7	Ph	(S_S,R_C)	***ent*-10**	93:7	73
					

[a] Product drawn and numbered is major isomer obtained. [b] Major isomer listed first. [c] Reaction was performed with LiOMe as the nucleophile. [d] E-acrylate was employed as the starting material.

in transition state **A** for the S_C-iodide and the sulfur to carbon bond forming reaction occurs through attack of the carbon bearing the iodide (Figure 1). In the proposed transition state, it is anticipated that the leaving iodide would be nearly eclipsing the equatorial substituent of the stereogenic carbon. Given the stereochemistry of the electrophile, transition state **A** holds the electrophile's R group axial, and the H is equatorial, thereby minimizing the effect of the eclipsing interaction. In such an arrangement, the selectivity of the alkylation occurs by placing the sulfur's R^1 group in an equatorial position away from the axial R group of the electrophile, avoiding a 1,3-diaxial interaction. The stereoselectivity of the alkylation arises since the R_C-iodide requires an adaptation of **A** where the R group on the chiral carbon creates an unfavorable eclipsing interaction with the iodide. Hence the transition state adopted for R_C-iodide alkylation is the enantiomer of **A**.

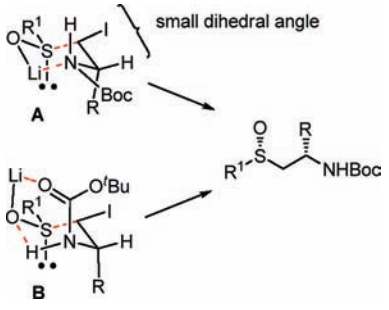


Figure 1. Orientations and interactions for the alkylation of the sulfenate sulfur.

(18) A related phenomenon has been observed wherein a proximal heteroatom enhances the yield of zinc sulfenate addition to an alkyne. See: Maezaki, N.; Yagi, S.; Yoshigami, R.; Maeda, J.; Suzuki, T.; Ohsawa, S.; Tsukamoto, K.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5550.

(19) Alkanesulfenates generated by this method generally decompose as the temperature approaches rt. See ref 14.

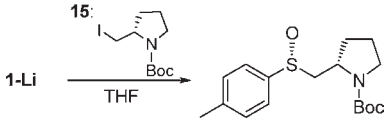
(20) (a) Lewanowicz, A.; Lipinski, J.; Siedlecka, R.; Skarzewski, J.; Baert, F. *Tetrahedron* **1998**, *54*, 6571. (b) Garcia Ruano, J. L.; Alcudia, A.; Del Prado, M.; Barros, D.; Maestro, M. C.; Fernandez, I. *J. Org. Chem.* **2000**, *65*, 2856.

(21) The absolute configurations of **10** (R_S, S_C) and ***ent*-10** (S_S,R_C) were assigned based on the identical match to the known literature values for **10** (+115.0; see ref 20a). Other rotations were consistent with the general trends of (R_S,S_C)-amino sulfoxides and (S_S,R_C)-amino sulfoxide as indicated in ref 20a. Further corroboration comes with the rotation value of the (R_S,R_C) isomer of **8** (ref 20b).

Alternatively, a primary H-bonding interaction may be preferred as in transition state **B**, with a secondary requirement for Li complexation to the Boc oxygen. Such an arrangement would also be consistent with the observed products, and both transition states call upon involvement of the lithium counterion as demanded by the results from the 12-crown-4 experiment.

To address the question as to whether H-bonding is involved or not, the N-methylated analog of **3** was selected as an electrophile that would permit alkylation without opportunity for H-bonding. However, attempts to convert Boc-protected (*S*)-2-(methylamino)-3-phenylpropyl alcohol to its iodide led to decomposition of the Boc unit and oxazoline formation. As an alternative that maintains some structural similarities, L-prolinol was converted to its corresponding iodide (**15**). The reaction of **1-Li** with **15** provided 61% of amino sulfoxide **16**, with a dr of 95:5 (Scheme 2). A single crystal X-ray structure analysis confirmed the configuration of the major isomer to be (R_S, S_C),[22] consistent with the stereochemistry of other alkylations with S_C-amino iodides. The high diastereoselectivity indicates that H-bonding is not a significant requirement for diastereoselection and that complexing to the heteroatom lone pair should be adequate to direct the stereochemistry in this and the other examples.

Scheme 2. Alkylation of Lithium *p*-toluenesulfenate (**1-Li**) with L-Prolinyl Iodide (**15**)



16 (61%, dr = 95:5)

Chiral β-amino sulfoxides have found utility as chiral ligands,[23] as effective organocatalysts[24] and in the synthesis of biologically or medicinally important compounds.[25] Although various methods are available for their synthesis,[20b] the sulfenate chemistry presented herein should be evaluated against oxidation of amino sulfanes.[23a,c,26] The key difference is that the stereocenter influences oxygen delivery in the oxidation protocol, whereas, in this chemistry, the chirality influences carbon−sulfur bond formation of an already monoxidized sulfur. Although the diastereoselective oxidation of enantiopure amino sulfides has been utilized extensively as a general method for amino sulfoxide formation, the existing protocols do not deliver dr's as consistently high as reported herein. The potential preference of sulfenate chemistry for this purpose is particularly realized when compared to an example where *two* chiral influences are required to deliver dr's as high as 93.5:6.5 in 59% yield.[26d]

To summarize, it has been shown that aromatic sulfenate anions can be alkylated by chiral β-amino iodides with high diastereoselectivity. Moreover, the reaction is stereospecific when considered from the perspective of the electrophilic (*R*)- and (*S*)-iodides. The alkylation chemistry demonstrates a conceptually novel mode for the creation of sulfur stereogenicity. Based on the examples shown, the S-functionalization of the prochiral sulfenates holds the potential to be superior to sulfur oxidation for the preparation of β-amino sulfoxides. An internal complexation of the lithium counterion with the electrophile's nitrogen is proposed to play a key role in the stereoselection.

It should also be noted that a new family of sulfenate electrophiles has been uncovered; the electrophile exhibits increased reactivity based on the nature of remote substitution, rather than on the degree of substitution or identity of the leaving group at the electrophilic carbon. We are exploring the substitution chemistry of a larger set of electrophiles and sulfenates to establish the scope of the chemistry and other influences on the stereoselectivity.

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Supporting Information Available. Experimental procedures and characterization data for products; X-ray crystal structure data including .cif file. This material is available free of charge via the Internet at http://pubs.acs.org.

(22) There is 7% disorder in the crystal due to the presence of the minor isomer in the recrystallized sample (post HPLC analysis). See Supporting Information. The crystal structure has been deposited at the CCDC (# CCDC 827867).

(23) (a) Petra, D. G. I.; Kamer, P. C. J.; Spek, A. L.; Schoemaker, H. E.; Van Leeuwen, P. W. N. M. *J. Org. Chem.* **2000**, *65*, 3010. (b) Wojaczynska, E.; Zielinska-Blajet, M.; Turowska-Tyrk, I.; Skarzewski, J. *Tetrahedron: Asymmetry* **2010**, *21*, 853. (c) Ekegren, J. K.; Roth, P.; Kallstrom, K.; Tarnai, T.; Andersson, P. G. *Org. Biomol. Chem.* **2003**, *1*, 358. (d) Pettinari, C.; Pellei, M.; Cavicchio, G.; Crucianelli, M.; Panzeri, W.; Colapietro, M.; Cassetta, A. *Organometallics* **1999**, *18*, 555. (e) Hiroi, K.; Sone, T. *Curr. Org. Synth.* **2008**, *5*, 305. (f) Wojaczynska, E.; Zielinska-Blajet, M.; Turowska-Tyrk, I.; Skarzewski, J. *Tetrahedron: Asymmetry* **2010**, *21*, 853. (g) Corbi, P. P.; Massabni, A. C.; Sabeh, L. P. B.; Costa-Neto, C. M. *J. Coord. Chem.* **2008**, *61*, 2470.

(24) (a) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133. (b) De, S. V.; Acocella, M. R.; Villano, R.; Scettri, A. *Tetrahedron: Asymmetry* **2010**, *21*, 1432.

(25) (a) Raghavan, S.; Krishnaiah, V.; Sridhar, B. *J. Org. Chem.* **2010**, *75*, 498. (b) Ma, D.; Zou, B.; Zhu, W.; Xu, H. *Tetrahedron Lett.* **2002**, *43*, 8511. (c) Huang, X.; Chen, D.; Wu, N.; Zhang, A.; Jia, Z.; Li, X. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4130. (d) Raghavan, S.; Krishnaiah, V. *J. Org. Chem.* **2010**, *75*, 748.

(26) (a) Brunet, E.; Gallego, M. T.; Garcia, R. J. L.; Parellada, D.; Rodriguez, J. H.; Urbano, A. *Tetrahedron* **1988**, *44*, 1421. (b) Dureault, A.; Carreaux, F.; Depezay, J. C. *Synthesis* **1991**, 150. (c) Nakajima, N.; Enomoto, T.; Matsuura, N.; Ubukata, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3331. (d) Nakajima, N.; Enomoto, T.; Watanabe, T.; Matsuura, N.; Ubukata, M. *Biosci., Biotechnol., Biochem.* **2003**, *67*, 2556. (e) Raghavan, S.; Rajender, A. *Tetrahedron* **2004**, *60*, 5059. (f) Siedlecka, R.; Skarzewski, J. *Synlett* **1996**, 757. (g) Quinet, C.; Sampoux, L.; Marko, I. E. *Eur. J. Org. Chem.* **2009**, 1806. (h) Meese, C. O. *Arch. Pharm. (Weinheim, Ger.)* **1987**, *320*, 473. (i) Van, d. B. L. A. G. M.; Lazaro, E.; Zylicz, Z.; Fennis, P. J.; Missler, F. A. N.; Lelieveld, P.; Garzotto, M.; Wagener, D. J. T.; Ballesta, J. P. G.; Ottenheijm, H. C. J. *J. Med. Chem.* **1989**, *32*, 2002.