The Endocyclic Restriction Test: The Geometries of Nucleophilic Substitutions at Sulfur(VI) and Sulfur(II)[†]

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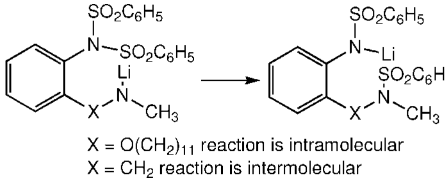

The trajectories for nucleophilic substitutions at sulfur(VI) and sulfur(II) have been investigated by the endocyclic restriction test. On the basis of double-labeling experiments, the sulfur(VI) transfer in the conversion of **1** to **2** is found to be intramolecular, while the sulfur(VI) transfer in the conversion of **3** to **4** and the sulfur(II) transfer in the conversion of **5** to **6** are found to be intermolecular. These results are taken to be consistent with transition structures for these sulfur transfer reactions which require a large angle between the entering and leaving group, a geometry analogous to apical group positions in trigonal bipyramidal transition states.

Introduction

Substitutions at sulfur are of interest in chemistry and biology.[1] The limiting pathways which describe the mechanistic possibilities of initial ionization, concerted displacement, or addition−elimination differ in the timing of bond making and bond breaking, the number of elementary steps, and the possible geometries of the transition structures.

Previous investigations of nucleophilic substitutions at sulfur(VI) and sulfur(II) have supported different pathways. These mechanisms include sulfenium and sulfonium cationic intermediates[2,3] as well as trigonal bipyramidal sulfuranes as intermediates or transition structures.[4−6,7e] The generally invertive course for sulfur(VI) substitutions is consistent with the latter, although competing retentive reactions have also been noted. Sulfonyl (S(VI)) transfers have been observed within four- and five-membered endocyclic rings, which would not allow the simultaneous apical entering and leaving groups of trigonal bipyramidal transition structures. However, a similar sulfonyl transfer was found not to occur in a six-membered endocyclic ring. Both addition−elimination and large angle transition structures have been reported for sulfenyl (S(II)) substitutions.[8]

We now report applications of the endocyclic restriction test to evaluate the geometries of nucleophilic substitutions at

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[†] Dedicated to the memory of Professor Albert I. Meyers, an outstanding scientist, a generous colleague, and a wonderful friend.

(1) (a) Cremlyn, R. *An Introduction to Organosulfur Chemistry*; John Wiley & Sons: New York, 1996. (b) *Perspectives in the Organic Chemistry of Sulfur*; Elsevier: New York, 1987. (c) *Organic Sulfur Chemistry*; Elsevier: New York, 1985.

(2) (a) Do, Q. T.; Elothmani, D.; Guillanton, G. L. *Tetrahedron Lett.* **1998**, *39*, 4657–4658. (b) Kobayashi, K.; Sato, S.; Horn, E.; Furukawa, N. *Tetrahedron Lett.* **1998**, *39*, 2593–2596.

(3) (a) Cox, R. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1743. (b) Kutuk, H.; Bekdemir, Y.; Soydas, Y. *J. Phys. Org. Chem.* **2001**, *14*, 224–228.

(4) (a) Bunton, C. A.; Hendy, B. N. *J. Chem. Soc.* **1962**, 2562. (b) Kaiser, E. T. *Acc. Chem. Res.* **1970**, *3*, 145–151. (c) Oae, S.; Fukumoto, R.; Kiritani, R. *Bull. Chem. Soc.* **1963**, *36*, 346–348.

(5) For examples of linear free energy studies of sulfur substitution, see: (a) Wilson, J. M.; Bayer, R. J.; Hupe, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 7922–7926. (b) Ciuffarin, E.; Fava, A. *Prog. Phys. Org. Chem.* **1968**, *6*, 81–109. (c) Biasotti, J. B.; Andersen, K. K. *J. Am. Chem. Soc.* **1971**, *93*, 1178–1182. (d) Choi, J. H.; Lee, B. C.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2002**, *67*, 1277–1281. (e) Baxter, N. J.; Rigoreau, L. J. M.; Laws, A. P.; Page, M. I. *J. Am. Chem. Soc.* **2000**, *122*, 3375–3385. (f) Andersen, K. K.; Bray, D. D.; Chumpradit, S.; Clark, M. E.; Habgood, G. J.; Hubbard, C. D.; Young, K. M. *J. Org. Chem.* **1991**, *56*, 6508–6516.

(6) For examples of calculations of sulfur substitutions, see: (a) Bachrach, S. M.; Hayes, J. M.; Dao, T.; Mynar, J. L. *Theor. Chem. Acc.* **2002**, *107*, 266–271. (b) Lee, I.; Kim, C. K.; Li, H. G.; Sohn, C. K.; Kim, C. K.; Lee, H. W.; Lee, B.-S. *J. Am. Chem. Soc.* **2000**, *122*, 11162–11172. (c) Bachrach, S. M.; Mulhearn, D. C. *J. Phys. Chem.* **1996**, *100*, 3535–3540. (d) Cameron, D. R.; Thatcher, R. J. *J. Org. Chem.* **1996**, *61*, 5986–5997. (e) Bachrach, S. M.; Woody, J. J.; Mulhearn, D. C. *J. Org. Chem.* **2002**, *67*, 8983.

(7) (a) Johnson, C. R.; Jonsson, E. U.; Wambsgans, A. *J. Org. Chem.* **1979**, *44*, 2061–2065. (b) Mikolajczyk, M.; Drabowicz, J. *Top. Stereochem.* **1992**, *13*, 333. (c) Wudl, F.; Lee, T. B. K. *J. Am. Chem. Soc.* **1973**, *95*, 6349–6358. (d) Oae, S.; Yokoyama, M.; Furakawa, N. *Tetrahedron Lett.* **1968**, *38*, 4131–4134. (e) Andersen, K. K.; Chumpradit, S.; McIntyre, D. J. *J. Org. Chem.* **1988**, *53*, 4667–4675. (f) Hellwinkel, D.; Supp, M. *Chem. Ber.* **1976**, *51*, 1525–1529. (g) Baxter, N. J.; Laws, A. P.; Rigoreau, L.; Page, M. *Chem. Commun.* **1997**, *2037*, 2038.

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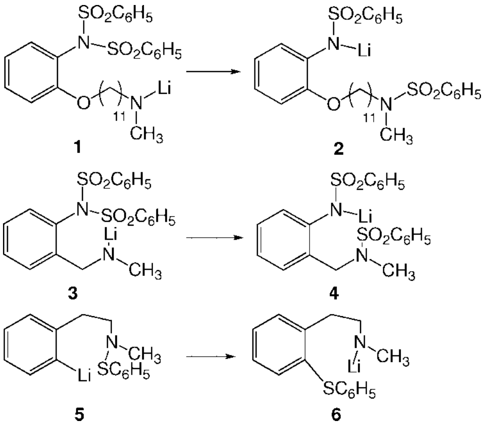
SCHEME 1



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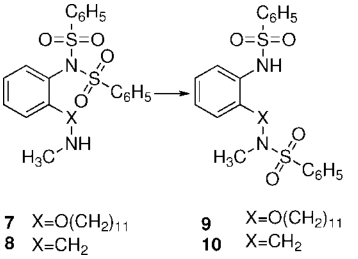

sulfur(VI) and sulfur(II). In this approach, linking a nucleophile to a sulfur bearing a leaving group through a tether places a restrain in the geometry of a possible intramolecular transfer. A short tether would not allow simultaneous disposition of an apical nucleophile and leaving group within an endocyclic ring, and the reaction would be expected to proceed intermolecularly. A long tether, however, would make such a transition structure accessible, and intramolecular transfer could become the reaction pathway.[9] An initial dissociative pathway would have a molecularity which would be independent of tether length. The sulfur transfers we have investigated are **1** to **2** and **3** to **4** for sulfur(VI) and **5** to **6** for sulfur(II) (Scheme 1).

Results and Discussion

Endocyclic Restriction Test at Sulfur(VI). The conversions of the aryl sulfonamides **7** and **8** to alkyl sulfonamides **9** and **10** (Scheme 2) via **1** to **2** and **3** to **4** involve sulfur(VI) transfers which could occur within a 17-membered or 6-membered endocyclic ring, respectively. The molecularity of these reactions has been investigated by double labeling experiments.

Syntheses of Sulfonamides 7−10. The long tethered substrate **7** was prepared in 10 steps (Scheme 3). The conversion of **11** to **15** via **12** to **13**, and **14** followed standard procedures as shown. From **15**, Boc protection to **16** followed by carbamate methylation provided **17**. Reduction of the nitro group to give the amine **18** was followed by a two-step protocol for the bis-sulfonylation to afford **19** and subsequently **20**. Deprotection of the carbamate completed the synthesis of **7**.

The synthesis of sulfonamide **8** (Scheme 4) was accomplished in 37% yield over five steps from **21**. The amine−borane complex **22** was converted to the benzyl amine **23**. Protection as the *tert*-butyl carbamate, followed by installation of both sulfonyl groups, provided **25** via **24**. Removal of the carbamate completed the synthesis of **8**.

Intermediate **19** was used for the independent synthesis of **9** via **26** as shown in Scheme 5.

Direct sulfonylation of **23** with benzenesulfonyl chloride provided **10** (Scheme 6) in 46% yield, along with mono- and trisulfonylated products.

Transfer of Sulfonyl Sulfur(VI): Conversions of 7 to 9 and 8 to 10. The sulfonyl transfers were carried out by deprotonations with lithium tetramethylpiperidine (LiTMP). From **7** and **8**, **9** and **10** could be isolated in 19% and 29% yields, respectively (Scheme 7). These reactions proceed via the conversions of **1** to **2** and **3** to **4**, respectively.

Synthesis of Labeled Sulfonamides 9 and 10. Isotopically substituted **7** and **8** required for double-label crossover experiments were prepared by the reactions used for the unlabeled compounds using deuterium labeled benzene sulfonyl chloride.

For the synthesis of labeled **7**-d_{10}, benzene-d_6 (99.6% isotopically enriched) was allowed to react with deuterosulfuric acid followed by treatment with thionyl chloride to give **27**-d_5 (Scheme 8).

Sulfonylation of **18** with **27**-d_5 gave **19**-d_5. Deprotonation with NaH and reaction with **27**-d_5 provided **20**-d_{10}. Standard Boc deprotection completed the synthesis of **7**-d_{10} (Scheme 9).

For the synthesis of **8**-d_{10}, the direct chlorosulfonation of benzene d_6 was used to prepare **27**-d_5 which was used in the standard sulfonylation of **24** to give labeled **25**-d_{10} (Scheme 10). Deprotection of **20**-d_{10} gave deuterium-labeled **7**-d_{10}. Although mass spectral analysis showed that deuterium incorporation was incomplete, presumably due to extensive exchange of deuterium for protium in the initial reaction, **7**-d_{10} was sufficiently labeled to give a definitive result in the double-labeling experiment.

Double-Labeled Crossover Experiments: Endocyclic Restriction Tests with 7 and 8. The molecularities for the conversions of **7** to **9** and **8** to **10** were determined by double-labeling crossover experiments. Shown in Scheme 11 are the possibilities for a mixture of unlabeled and fully labeled compounds. If the phenylsulfonyl transfer is intramolecular, there will be no crossover of label, and the products will have the same double-labeled and unlabeled distribution as the starting mixture. If the phenylsulfonyl transfer is intermolecular, there will be crossover, and the products will be doubly, singly and unlabeled in a statistical ratio relative to the starting mixture.

A double-labeled crossover experiment was performed with **7** and **7**-d_{10} to test the molecularity of phenylsulfonyl transfer with the long-tethered substrate, and these results are presented in Table 1. Treatment of an equimolar mixture of **7** and **7**-d_{10} with LiTMP at 0.1 and 0.01 M followed by isolation of **9** and analysis of isotopic composition by FABMS gave the results shown in Table 1. Table 1 also shows the results expected for intramolecular and intermolecular phenylsulfonyl transfer.

The data show that when the crossover reaction was carried out at a concentration of 0.1 M, the transfer of the sulfonyl

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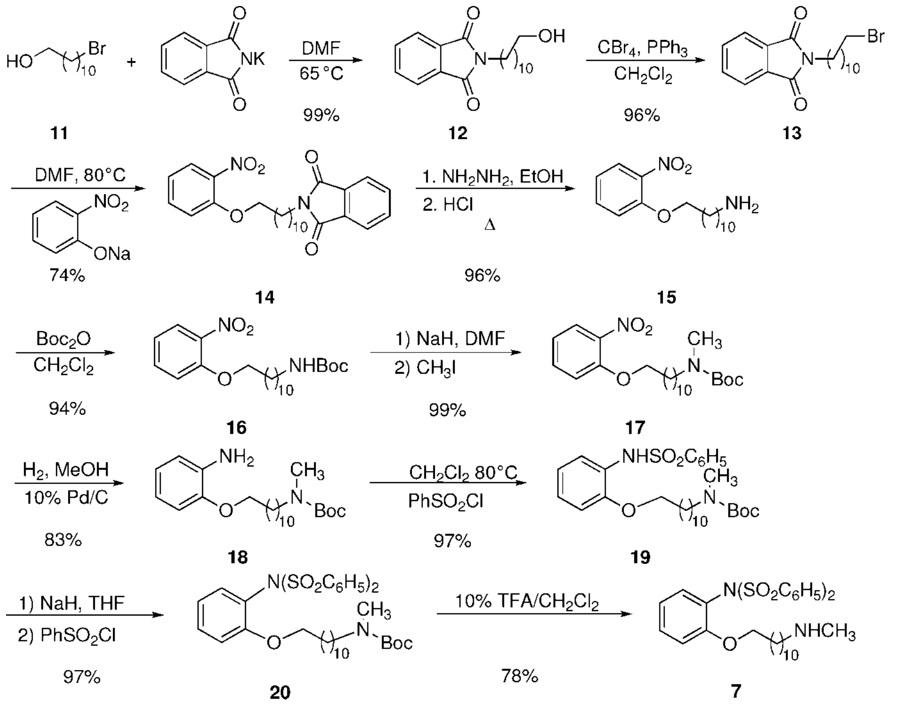
(8) (a) Hogg, D. R.; Vipond, P. W. *J. Chem. Soc. C* **1970**, 2142–2144. (b) Rosenfield, R. C., Jr.; Parthasarathy, R.; Dunitz, J. D *J. Am. Chem. Soc.* **1977**, 4860. (c) Singh, R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 6340. (d) Luczak, L.; Lopusinski, A.; Michalski, J. *Tetrahedron* **1998**, *54*, 9731. (e) Fachini, M.; Lucchini, V.; Modena, G.; Pasi, M.; Pasquato, L. *J. Am. Chem. Soc.* **1999**, *121*, 3944–3950.

(9) Lee, S. J.; Terrazas, M. S.; Pippel, D. J. *J. Am. Chem. Soc.* **2003**, *125*, 7307, and references cited therein for other cases using the endocyclic restriction test. The data from double-labeling experiments provide definitive distinctions between intermolecular and intramolecular pathways for these sulfur transfers. Assignments for the favored geometries for atom-transfer reactions under this test are conclusive and independent of yields. Low yields of the atom-transferred products or the operation of pathways which give other products do not compromise the test under this protocol.

SCHEME 3



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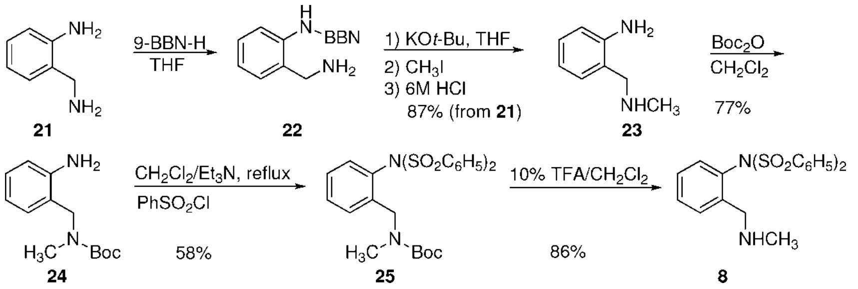

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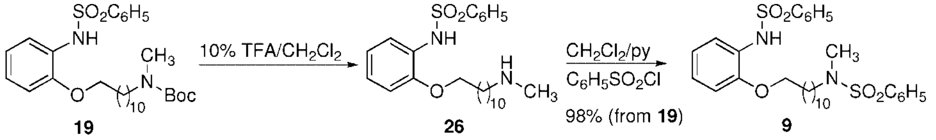

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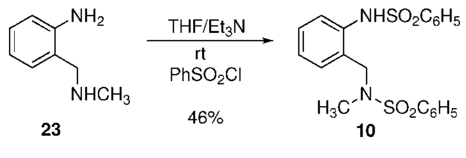

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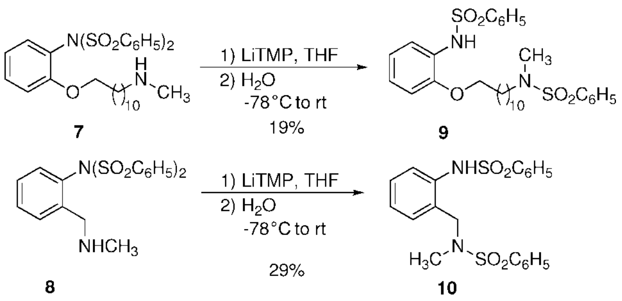
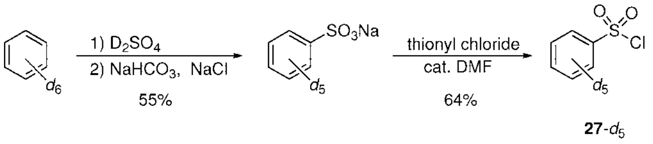


group occurs by both an intramolecular and intermolecular pathway. At the dilution of 0.01 M, however, the product distribution changes to reveal a significant increase in intramolecular substitution. This increase on dilution is consistent with a first-order intramolecular reaction which becomes competitive with a second-order intermolecular reaction at the higher concentration.

A double-labeled crossover experiment with the short-tethered substrate was carried out by treatment of a 0.01 M mixture of **8** and **8**-d_n with LiTMP. The isotopic distributions of **8** and **10** as determined by FABMS, along with those expected for a completely intramolecular and intermolecular transfer, are shown in Table 2.[10] The incomplete labeling of **8**-d_n leads to a wide distribution of label, but the results are definitive.

The results in Tables 1 and 2 show that under the same conditions the conversion of **7** to **9** via **1** to **2** can be an intramolecular reaction, whereas the conversion of **8** to **10** via **3** to **4** is intermolecular.

SCHEME 8



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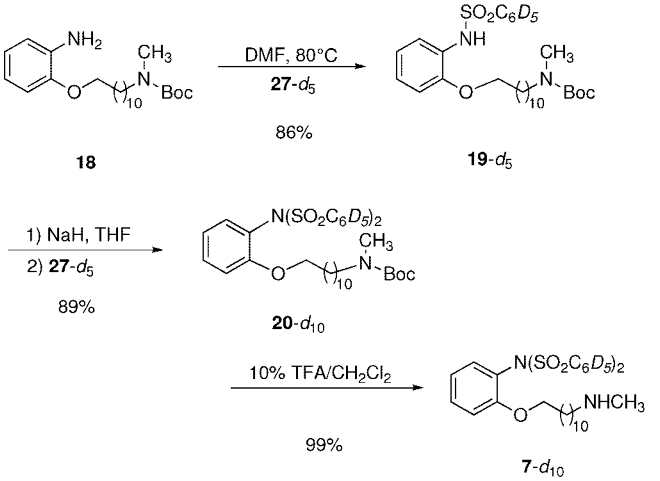

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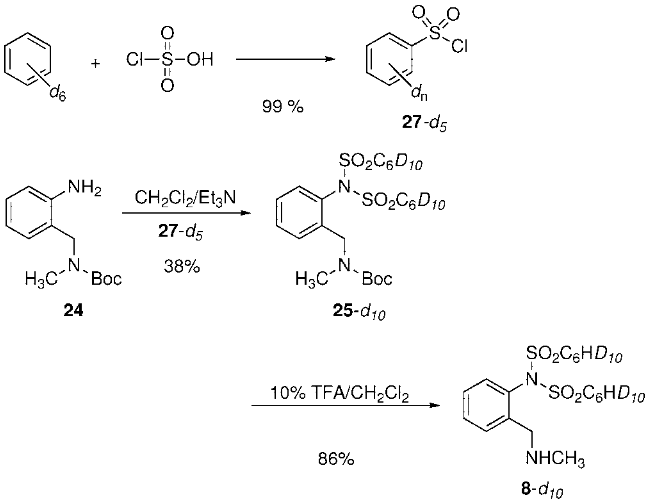


The results rule out mechanisms that do not require an almost linear arrangement of the entering and leaving nitrogen about sulfur in these phenylsulfonyl transfers. That the putative transition state is reasonably a trigonal bipyramidal structure in which a large bond angle between the entering and leaving groups is required for product formation is consistent with previous experimental work. [7]

Endocyclic Restriction Test at Sulfur(II). The conversion of the sulfenamine **28** to sulfide **29** (Scheme 12) via **5** to **6** involves a transfer of sulfur(II) which could occur within a 6-membered endocyclic ring. The molecularity of this substitution has been investigated by a double-labeled crossover experiment with **28** and **28**-d_8.

SCHEME 11

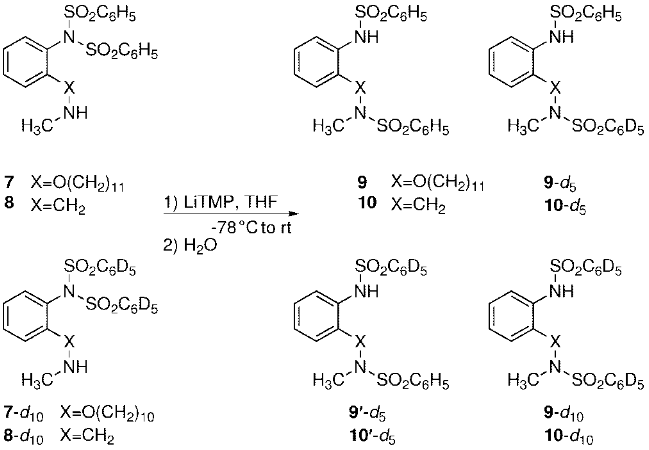


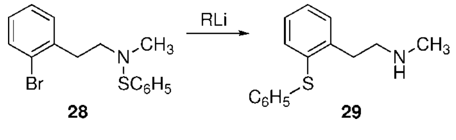
TABLE 1. Isotopic Ratios for the Double-Labeled Endocyclic Restriction Test Conversion of 7 to 9 at 0.01 M

		7-d_n		9-d_n	
		Experimental		theoretical	
d_n		0.1 M	0.01 M	intramolecular	intermolecular
d_0	50	33	48	50	25
d_4	0	2	1	0	1
d_5	0	32	7	0	49
d_9	2	3	2	2	1
d_{10}	48	30	42	48	24

TABLE 2. Isotopic Ratios for the Double-Labeled Endocyclic Restriction Test Conversion of 8 to 10 at 0.01 M

	8-d_n		10-d_n	
	experimental		theoretical	
d_n		0.01 M	intramolecular	intermolecular
d_0	43	24	43	22
d_1	1	4	1	5
d_2	1	7	1	8
d_3	3	10	3	11
d_4	5	14	5	15
d_5	7	15	7	17
d_6	9	6	9	5
d_7	10	6	10	6
d_8	10	6	10	5
d_9	7	5	7	4
d_{10}	4	3	4	2

SCHEME 12



Synthesis of Sulfenamides 28 and 29. The synthesis of **28** was completed in five linear steps in 63% overall yield. Borane reduction of commercially available *o*-bromobenzyl nitrile (**30**) provided amine **31**, which was converted to the *N*-Boc carbamate **32**. Deprotonation and alkylation afforded the secondary carbamate **33**. The secondary amine **34**, obtained with 10% trifluoroacetic acid, allowed installation of the phenylsulfenyl group with *S*-phenylthiophthalimide to provide **28** (Scheme 13).

From commercially available **35**, the synthesis of **29** was completed in five steps (Scheme 14) in 91% yield (Scheme 14). Borane reduction of the nitrile **35** and subsequent carbamate protection gave **37** via **36**. Standard alkylation using NaH and

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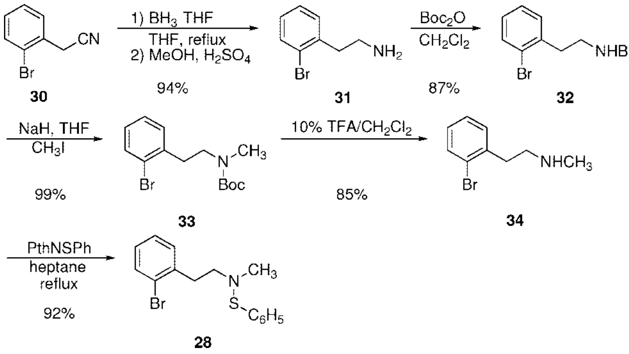
(10) In earlier runs, **8**-d_n had tended to rearrange prior to mixing with **8**. Careful purification of each component and analysis was carried out to show this did not occur prior to the reaction. The fact that there was not scrambling of the labels in the conversion of **7** to **9** under the same conditions establishes that label scrambling prior to phenyl sulfonyl transfer is not occurring in this case.

SCHEME 13



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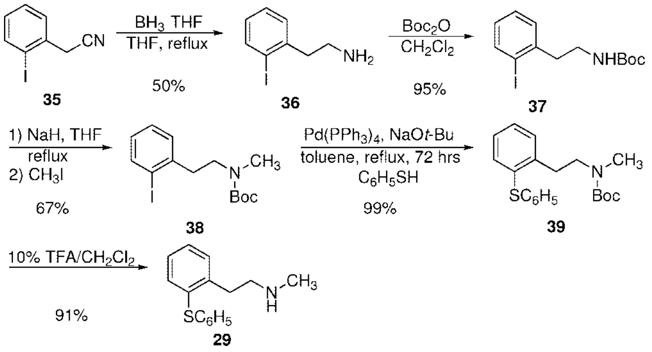

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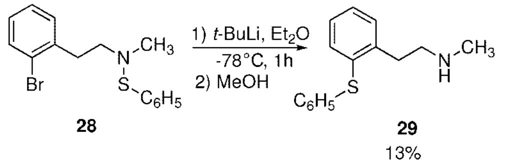
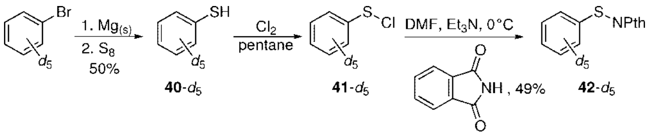


SCHEME 16



iodomethane provided **38**. The diaryl sulfide functionality was installed through palladium-catalyzed cross-coupling of **38** with thiophenol to give **39**, which on standard deprotection afforded **29**.

Transfer of Sulfenyl Sulfur(II): Conversions of 28 to 29. Lithium−bromide exchange of **28** with *t*-BuLi provided the carbanion nucleophile for sulfenyl group transfer of **5** to give **6** and then **29**. Treatment of **28** with 2.0 equiv of *t*-BuLi in diethyl ether at −78 °C for 1 h provided **29** in 13% yield (Scheme 15).

Synthesis of Labeled 28. The preparation of **28**-d_8 was carried out from bromobenzene-d_5 following standard procedures. Labeled phenylmagnesium bromide was treated with elemental sulfur to provide crude **40**-d_5, which was allowed to react with chlorine gas to provide **41**-d_5. Conversion to **42**-d_5 was completed by reaction with phthalimide and triethylamine in DMF (Scheme 16).

Alkylation of **32** with iodomethane-d_3 provided **33**-d_3 with high deuterium incorporation, as determined by both ^{1}H NMR and FD-MS analysis. Deprotection to **34**-d_3 and sulfenylation using **42**-d_5 provided **28**-d_8 (Scheme 17).

SCHEME 17

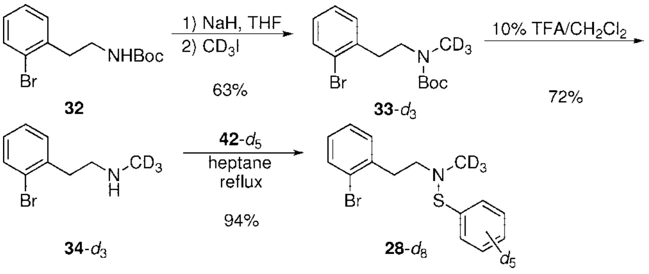
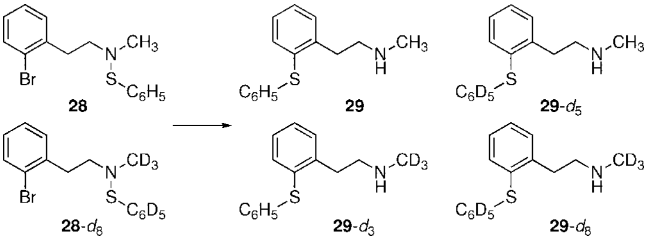


TABLE 3. Isotopic Ratios for the Endocyclic Restriction Test Conversion of 28 to 29 at 0.1 M

		29			
		experimental		theoretical	
d_n	**28**-d_n	0.1 M	0.01 M	intramolecular	intermolecular
d_0	41	21	23	41	20
d_3	4	27	25	4	25
d_5	4	23	26	4	25
d_8	52	29	26	52	31

SCHEME 18



Double-Labeled Crossover Experiments: The Endocyclic Restriction Test with 28. The reaction of a mixture of **28** and **28**-d_8 would produce a statistical mixture of unlabeled **29**, **29**-d_3, **29**-d_5, and **29**-d_8 from an intermolecular transfer, while an intramolecular reaction would provide only **29** and **29**-d_8 with an isotopic ratio the same as that of the reactants.

Mixtures of **28**, **28**-d_3, **28**-d_5, and **28**-d_8 were submitted to the reaction conditions at 0.1 and 0.01 M. The isotopic distributions of **28** and **29** as determined by mass spectral analysis are shown in Table 3, along with the results expected for intramolecular and intermolecular transfer (Scheme 18). Recovery of unreacted starting material showed no isotopic exchange had occurred to the mixture of **28**, **28**-d_3, **28**-d_5, and **28**-d_8.

The conversion of **5** to **6** as indicated by the compositions of **28** and **29** show the reaction is intermolecular under these conditions. These results are consistent with a requirement of a linear transition state of the entering carbon nucleophile and the nitrogen leaving group in this sulfur(II) transfer.[11]

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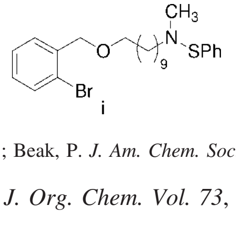
(11) Our efforts to investigate a long-chain tether for sulfur(II) by the investigation of i were not successful (Jarboe, S. Ph.D. Thesis, University of Illinois, 2002). Absent the experimental results for that case, it could be argued that there is insufficient dilution in these experiments for a definitive conclusion. Our preference, consistent with previous work, is to favor a linear transition structure.[8a]



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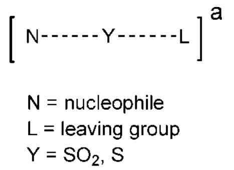
(12) Tollefson, M. B.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 9052.

Conclusion

From the present work, the reaction pathways for sulfur(VI) and sulfur(II) group transfers in nucleophilic substitutions may be considered to favor a linear transition structure represented by **30**. This classic transition state structure, long established for S_N2 nucleophilic substitutions at sp^3-hybridized carbon, is also consistent with the geometrical requirements for substitution at nitrogen, oxygen, bromine, and chlorine.[9] Nucleophilic substitution at phosphorus has been shown to be able to proceed through an addition−elimination process in which the geometry of the transition structure is not always required to be linear.[12] Nonetheless, simultaneous linear orientation of the incoming nucleophile and the leaving group analogous to trigonal bipyramidal transition structures for nucleophilic displacements can be considered to be the favored pathway for transfer of atoms in the upper right-hand corner of the periodic table.



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Experimental Section

The compounds synthesized were determined to be >95% pure by ^{1}H NMR and ^{13}C NMR analysis as well as by elemental analysis in selected cases. The products of the endocyclic restriction tests were identified by comparisons of NMR spectra and GC retention times with the authentic materials described below and in the Supporting Information. The isotopic compositions were determined by FI/MS.

***N*-Methyl-11-(2-(*N*,*N*-bisphenylsulfonyl)aminophenoxy)undecylamine (7).** To a solution of 0.75 g (1.11 mmol) of **20** in 10 mL of CH_2Cl_2 was added 1 mL of trifluoroacetic acid. The solution immediately turned from clear to an orange color and was allowed to stir at room temperature for 16 h. The mixture was basified with 10% NaOH solution, extracted three times with CH_2Cl_2, and the combined organics were dried over $MgSO_4$. The drying agent was filtered and the solvent removed by distillation under reduced pressure leaving **7** as a clear yellow oil in 78% yield (0.50 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18−1.34 (m, 16H), 1.47 (m, 2H), 2.07 (br s, 1H), 2.42 (s, 3H), 2.56 (t, J = 7 Hz, 2H), 3.63 (t, J = 2H), 6.85 (dd, J = 8, 1 Hz, 1H), 6.91 (td, J = 8,1 Hz, 1H), 7.10 (dd, J = 8, 2 Hz, 1H), 7.37 (ddd, J = 8, 7, 2 Hz, 1H), 7.49 (m, 4H), 7.62 (tt, J = 7, 1 Hz, 2H), 7.96 (m, 4H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 25.4, 27.2, 28.5, 29.2, 29.4, 29.4, 29.5, 29.5, 29.6, 36.2, 52.0, 68.2, 112.6, 120.2, 122.7, 128.5, 128.7, 131.9, 133.0, 133.4, 140.3, 157.3.

***N*-Benzenesulfonyl-*N*-(2-(*N*-benzenesulfonyl)aminobenzyl)undecylamine (9).** To a solution of 0.328 g (0.62 mmol) of **19** in 5 mL of CH_2Cl_2 was added 0.5 mL of trifluoroacetic acid. The solution immediately turned from clear to an orange color and was allowed to stir at room temperature for 6 h. The mixture was basified with 10% NaOH solution and extracted three times with CH_2Cl_2, and the combined organics were dried over $MgSO_4$. The drying agent was filtered and the solvent removed by distillation under reduced pressure leaving **26** as a white solid that was resuspended in 5 mL of CH_2Cl_2. To this solution was added 0.097 g (1.23 mmol) of pyridine and 0.114 g (0.65 mmol) of benzenesulfonyl chloride, and the solution was stirred at room temperature for 24 h. The solution was washed twice with 10% aqueous HCl. The combined aqueous portions were extracted two times with CH_2Cl_2, and the organics were dried over $MgSO_4$. The drying agent was removed by filtration and the solvent removed by distillation under reduced pressure leaving a clear viscous yellow oil. Purification by silica gel flash chromatography (20% EtOAc/petroleum ether) provided **9** as a clear colorless oil in 98% yield (0.346 g) for the two steps: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22−1.36 (m, 15H), 1.49−1.70 (m, 5H), 2.71 (s, 3H), 2.99 (t, J = 7 Hz, 2H), 3.72 (t, J = 7 Hz, 2H), 6.70 (d, J = 8 Hz, 1H), 6.89 (t, J = 8 Hz, 1H), 6.96 (s, 1H), 7.02 (t, J = 8 Hz, 1H), 7.38 (t, J = 8 Hz, 2H), 7.46−7.60 (m, 5H), 7.71 (d, J = 8 Hz, 2H), 7.78 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 25.9, 26.4, 27.5, 28.9, 29.1, 29.3, 29.4, 29.4, 34.5, 36.9, 50.1, 68.5, 111.3, 120.8, 121.8, 125.6, 125.7, 127.1, 127.3, 128.7, 129.0, 132.4, 132.8, 137.6, 139.2, 149.1. Anal. Calcd for $C_{29}H_{38}N_2O_5S_2$: C, 62.91; H, 7.04; N, 4.89. Found: C, 62.59; H, 6.97; N, 4.79.

Endocyclic Restriction Test for Sulfonyl Transfer for 7 and 7-d_{10}. To a solution of 0.149 g (0.260 mmol) of **7** and 0.151 g (0.260 mmol) of **7**-d_{10} at −78 °C was added 0.38 mL (0.571 mmol) of LiTMP (1.5 M in THF) in 5.2 mL of THF. The dry ice/acetone bath was removed and the solution stirred as it slowly warmed to room temperature for 16 h. The yellow mixture was diluted with 3 mL of brine and extracted three times with Et_2O. The combined organics were dried over $MgSO_4$. The drying agent was removed by filtration and the solvent removed by distillation under reduced pressure to give 275 mg of a thick orange oil. This mixture was purified by silica gel flash chromatography (30% EtOAc/petroleum ether as eluent) to give 57 mg (19%) of **9**.

Endocyclic Restriction Test for Sulfonyl Transfer for 8 and 8-d_{10}. To a solution of 0.040 g (0.281 mmol) of TMP in 5 mL of THF was added 0.164 mL (0.238 mmol) of *n*-BuLi (1.45M). The solution was stirred at room temperature for 10 min and subsequently cooled to −78 °C. By way of cannula, the LiTMP solution was transferred to a −78 °C solution of 45 mg (0.108 mmol) of **8** and 48 mg (0.108 mmol) of **8**-d_{10} in 215 mL of THF (concentration of solution = 0.01M). The dry ice/acetone bath was removed and the solution stirred as it slowly warmed to room temperature for 16 h. The yellow mixture was diluted with 20 mL of brine and extracted three times with Et_2O. The combined organics were dried over $MgSO_4$. The drying agent was removed by filtration and the solvent removed by distillation under reduced pressure to give 69 mg of a thick orange oil. The crude mixture was flash chromatographed through a silica gel column (30% EtOAc/petroleum ether as eluent) to give 7 mg of **10** (6%).

Endocyclic Restriction Test for Sulfur Transfer for 28 and 28-d_6. To a −78 °C solution consisting of 20.2 mg (0.078 mmol) of **28** and 20.7 mg (0.078 mmol) of **28**-d_6 in 1.55 mL (0.1 M) of Et_2O was added 0.193 mL (0.31 mmol) of *t*-BuLi (1.6 M). The solution was allowed to react at −78 °C for 1 h prior to being quenched with 100 μL of MeOH. After being warmed to room temperature, the mixture was diluted with 5 mL of water and subsequently extracted three times with Et_2O. The combined organics were dried over $MgSO_4$ and filtered, and the solvent was removed by distillation under reduced pressure to yield 20.0 mg of a pale yellow oil.

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

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