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Altering the Stereochemistry of Allylation Reactions of Cyclic α-Sulfinyl Radicals with Diarylureas

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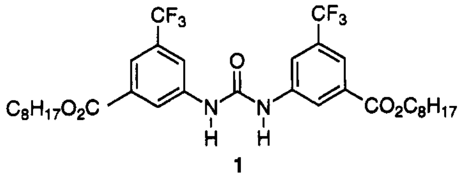
Summary: Radical allylations of 2-(phenylseleno)tetrahydrothiophene oxide and 2-benzyl-5-(phenylseleno)-3-isothiazolidone 1-oxide with allyltributylstannane in the presence of *N,N*-bis[3-(trifluoromethyl)-5-(carbooctyloxy)phenyl] urea have been investigated. This urea was shown to be about as selective at promoting formation of *trans*-2-allyltetrahydrothiophene oxide and *trans*-5-allyl-2-benzyl-3-isothiazolidone 1-oxide as hydrogen bonding solvents and Lewis acids.

The use of Lewis acidic additives is a time-tested strategy for altering rates and selectivities of ionic and pericyclic reactions that is only now being applied in radical reactions.[1] We now report that a new protic Lewis acid, diarylurea 1, can alter the rate and stereochemical outcome of the allylation reactions of cyclic sulfinyl radicals with allyltributylstannane. The choice of 1 was inspired by a report of Kelly and co-workers[2] showing that acidic bisphenol 2 could accelerate Diels–Alder reactions and by a crystal structure study of Etter and Reutzel showing that *m*-nitrodiaryl urea 3 formed crystalline complexes with all sorts of Lewis bases.[3] These bis-hydrogen-bonded complexes resemble hydrated structures 4 that Jorgensen has suggested to rationalize the accelerating effect of water on Diels–Alder and Claisen rearrangements.[4] Interesting reagents can be designed by combining the ideas and observations of Etter, Kelly, and Jorgensen. We modified 3 by replacing the nitro group (a radical inhibitor) with a trifluoromethyl group and by adding the octyl ester to facilitate the synthesis and to increase the solubility of 1. The synthesis of 1 is described in the supplementary material.[5] Details of the synthesis of a series of ureas and thioureas related to 1 and 3 and measurements of their abilities to bind both neutral and anionic molecules[6] will be reported separately.



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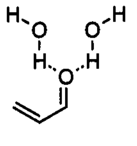
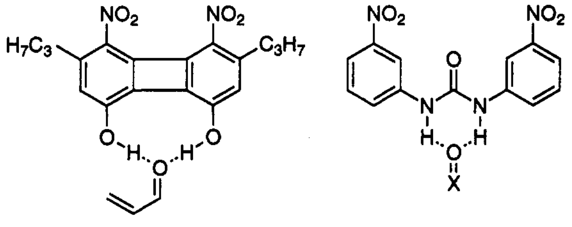


4 Jorgensen's hydration model



2 complex of Kelly's bis-phenol

3 complex of Etter's urea

Figure 1.

To evaluate the ability of 1 to alter the outcome of radical reactions, we turned to two recent reports of radical allylations of cyclic α-sulfinyl radicals. Renaud and Ribezzo[1a] reported that stereoselectivity in the reaction of α-(phenylseleno) sulfoxide 5 with allyltributylstannane was increased by the addition of organometallic Lewis acids (eq 1a) while Waldner, De Mesmaeker, and coworkers[7] found that stereoselectivities in radical allylations of 8a were enhanced when reactions were conducted in hydrogen bond donating solvents like ethanol and trifluorethanol. These reactions served as calibrations of effects of solvent and of traditional Lewis acids compared to urea 1.

We began with seleno sulfoxide 5, which was allylated by sunlamp photolysis with allyltributyl stannane at 15 °C.[1a] The first nine entries in Table 1 show the effects of solvents (entries 1–6) and traditional Lewis acids (entries 7–9) on the allylation of 5. These are corrected ratios that

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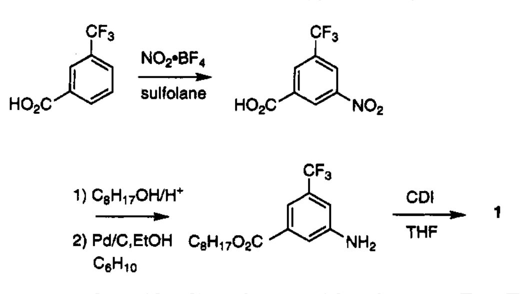
(1) (a) Renaud, P.; Ribezzo, M. *J. Am. Chem. Soc.* **1991**, *113*, 7803–05. (b) Newcomb, M.; Ha, C. *Tetrahedron Lett.* **1991**, *32*, 6493–96. (c) Guindon, Y.; Lavallée, J. F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701–02. (d) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300–02. (e) Toru, T.; Watanabe, Y.; Tsusaka, M.; Ueno, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10464–65.

(2) Kelly, T. R.; Meghani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990**, *31*, 3381–84.

(3) Etter, M. C.; Reutzel, S. M. *J. Am. Chem. Soc.* **1991**, *113*, 2586–98.

(4) (a) Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 10966–68. (b) Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 7430–32.

(5) (a) Several binding constants of related ureas with anions have already appeared. Smith, P. J.; Reddington, M. V.; Wilcox, C. S. *Tetrahedron Lett.* **1992**, *33*, 6085–88. (b) The synthesis of 1 is summarized below, and details are provided in the supplementary material.



(6) Recent studies of binding of ureas with anions: (a) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369–70. (b) Hamann, B. C.; Branda, N. R.; Rebek, J. R., Jr. *Tetrahedron Lett.* **1993**, *34*, 6837–40. (c) Smith, P. J.; Kim, E.; Wilcox, C. S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1648–50.

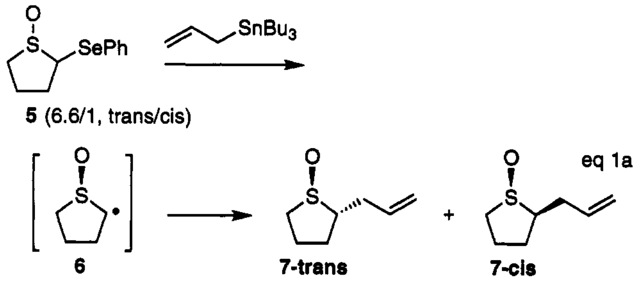
(7) Waldner, A.; De Mesmaeker, A.; Hoffmann, P.; Mindt, T.; Winkler, T. *Synlett* **1991**, 101–103.

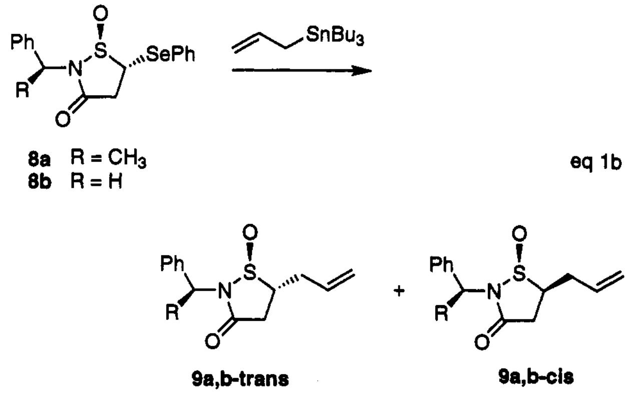
0022-3263/94/1959-3259$04.50/0

Table 1. Allylations of Phenylseleno Sulfoxide 5[a]

entry	solvent	additive	7-*trans*/7-*cis* (yield, %)
1	benzene[a]	none	2.5/1 (60)
2	CH_2Cl_2[a]	none	5.5/1 (62)
3	CH_3CH_2OH[b]	none	4.9/1 (87)
4	CH_3CO_2H[b]	none	6.7/1 (51)
5	CF_3CH_2OH[b]	none	8.1/1 (83)
6	THF[a]	none	2.2/1 (36)
7	THF[a]	LiCl (0.5 M)	5.8/1 (25)
8	THF[a]	$ZnBr_2$ (0.5 M)	8.0/1 (60)
9	THF[a]	BF_3·Et_2O (0.5 M)	4.5/1 (73)
10	benzene[a]	1 (0.2 equiv)	3.7/1 (57)
11	benzene[a]	1 (0.6 equiv)	5.8/1 (72)
12	benzene[a]	1 (1.0 equiv)	7.0/1 (81)

[a] This work: sulfoxide 6 [0.4 M], allyltributylstannane [0.5 M], additive, and AIBN were dissolved in the indicated solvent and irradiated with a sunlamp for 24 h at 15 °C. [b] Results taken from Renaud and Moufid, ref 1a.





differ from those originally reported,[1a] and the full details of a collaborative investigation of these reactions with Renaud's group will be reported separately.[8] The results of allylation of 5 in the presence of increasing amounts of 1 are summarized in Table 1, entries 10–12. These allylations were conducted under fixed conditions varying only the amount of 1. The reactions with 1 were all clean, and the balance of the material not accounted for in the yield of 7-*trans*/7-*cis* was unreacted seleno sulfoxide 5. Urea 1 was readily recovered by flash chromatography and was reused repeatedly. An increase in the amount of urea 1 increases both the trans/cis ratio and the combined yield of 7. The use of as little as 0.2 equiv of 1 provides a noticeable increase in the trans/cis ratio from 2.5/1 (entry 1) to 3.7/1 (entry 10) while the use of a stoichiometric amount of 1 increases the ratio to 7.0/1 (entry 12). The addition of 1 equiv of 1 provides stereoselectivity enhancements comparable to the best solvent and Lewis acid enhancements shown in Table 1.

We next investigated the effects of 1 as an additive in the Waldner/De Mesmaeker system.[7] Because the preparation of optically active **8a** requires a diastereomer separation, we elected instead to prepare racemic **8b**. This preparation was readily accomplished by following standard procedures,[7,9] as detailed in the supplementary material. Table 2 summarizes the results of allylations of **8b**, which were conducted at 55 °C for 24 h. Without additive (entry 1), the reaction in benzene was not complete after 24 h, and a 5.3/1 ratio of **9a**-*trans*/**9a**-*cis* was observed. In EtOH (entry 2), the reaction was faster and the selectivity was higher (9.8/1). Adding trifluoroethanol to the benzene solution (1 equiv, 5 equiv) also increased the selectivity to a similar level (entries 3 and 4). Adding increasing amounts of 1 (0.25 equiv, 0.5 equiv, 1.0 equiv) gradually increased the selectivity up to 14/1 (entries 5–7). Once again, the enhancing effect of just 1 equiv of 1 is superior to that of the H-bond donor solvent ethanol and the additive trifluoroethanol.

Table 2. Allylations of (Phenylseleno)isothiazolidine Oxide 8b[a]

entry	solvent	additive	**9b**-*trans*/**9b**-*cis*[b] (yield, %)[c]
1	benzene	none	5.3/1 (59)
2	EtOH	none	9.8/1 (63)
3	benzene	TFE (1.0 equiv)	7.1/1 (61)
4	benzene	TFE (5 equiv)	10.3/1 (63)
5	benzene	1 (0.25 equiv)	7.1/1 (70)
6	benzene	1 (0.5 equiv)	11.3/1 (72)
7	benzene	1 (1.0 equiv)	14.1/1 (72)

[a] **8b** [0.4 M], allyl tributylstannane [0.5 M], additive, and AIBN were heated in benzene at 55 °C for 24 h. Control experiments showed that **9b** did not equilibrate under these conditions. [b] Ratios determined by integration of the ^{13}C NMR spectra recorded in C_6D_6. [c] Isolated yield of **9b**-*trans*.

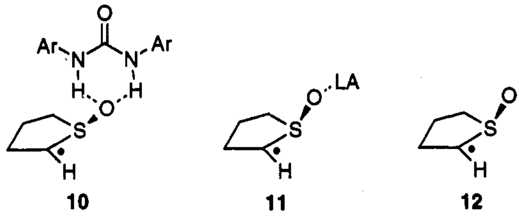


Figure 2.

These early results are consistent with the intermediacy of complexed radical 10 (Figure 2) reacting in competition with uncomplexed radical 6. The size of the urea helps shield one face, and this accounts for the increase in the trans/cis ratio. Supporting the intermediacy of 10 is the analogy to the allylation reactions of 1 with Lewis acids in hydrogen bond donor solvents, for which models like 11 and 12 have been proposed.[1a,7,8] Control experiments also support the intermediacy of 10. For example, allylation of 5 with 1 equiv of 1 in the presence of 5 equiv of tetrahydrothiophene oxide reduces the selectivity from 7.0/1 to 3.4/1. The *N,N*-dimethyl analog of 1, a urea lacking N–H bonds, has almost no effect on the allylation of 1 (2.5/1 with no additive, 2.9/1 with 1 equiv of dimethylurea). Complex 10 is also supported by the measurements of association constants. For example, by standard ^1H NMR titration experiments, we determined that the association constant of 1 with tetrahydrothiophene oxide was 1×10^3 M^{-1}. Thus, there is reasonable binding between 1 and sulfoxides, though one might intuitively expect that α-sulfinyl radicals will be poorer Lewis bases than the parent sulfoxides because the radicals are more electron deficient. The effects of 1 are not related to its Brönsted

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(8) Renaud, P.; Moufid, N.; Kuo, L. H.; Curran, D. P. *J. Org. Chem.*, in press.

(9) Lewis, S. N.; Miller, G. A.; Hausman, M.; Szanborski, E. C. *J. Heterocycl. Chem.* **1971**, *8*, 571–78.

acidity. Urea 1 must be a much weaker acid than typical carboxylic acids, but carboxylic acids do not bind well to sulfoxides and they have small effects on the allylation of 1.[8]

Secure explanations for the substoichiometric effect of 1 on the stereoselectivity and for the apparent ability of 1 to increase the rate of the radical chain reaction (as reflected by the increase percent yield) cannot yet be given. Assuming that 1 does not affect the rate of chain initiation, we can then propose that it may affect the rate of the slow propagation step, which is the radical addition. Complexed radical **10** may be more electrophilic than free radical **6**, and thus favorable polar effects may accelerate its rate of addition to allylstannane. It is not clear whether **10** and **6** are in equilibrium or whether complexed radical **10** must be generated from a complex of 1 with precursor **5**. The relative reactivity of complexed and free **5** toward tin radical is also unclear. Very recently, Renaud has discovered that Yamamoto's bulky aluminum phenoxides promote exceptional levels of stereoselectivity when used stoichiometrically and good levels of selectivity when used catalytically in these reactions.[8] Catalysis of radical reactions is quite challenging,[1b,10] and Renaud's results and ours hold out the promise that improved catalytic reagents and procedures can be developed.

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Supplementary Material Available: Procedures for synthesis and characterization (including copies of ^{1}H and ^{13}C NMR spectra) of **1**, **8**, and **9** and typical allylation (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(10) Singleton, D. A.; Huval, C. C.; Church, K. M.; Priestley, E. S. *Tetrahedron Lett.* **1991**, *32*, 5765–68.