Altering the Stereochemistry of Allylation Reactions of Cyclic α-Sulfinyl Radicals: Effects of Solvents and Lewis Acids

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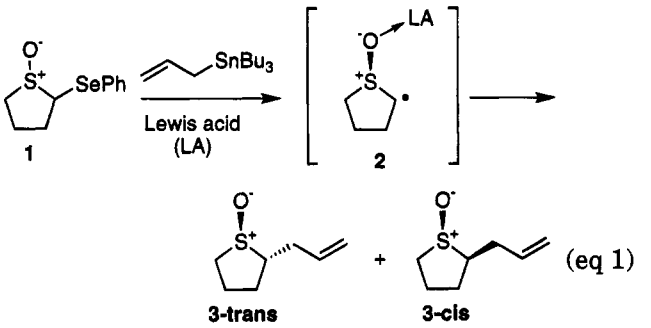
Full details of the stereochemical outcome of the allylation of the tetrahydrothiophene-2-yl 1-oxide radical in different solvents and in the presence of Lewis acids are reported. Corrections of the cis/trans ratios initially reported in the original communication are presented and the origin for the systematic overestimation of the ratio was found to be the decomposition of the minor cis diastereoisomer during the GC analysis. However, the originally reported stereoselectivity enhancements in the presence of Lewis acids are still valid, although the effects are of smaller amplitudes. The conclusions about an intermediate oxygen-complexed α-sulfinyl radical stand. We report that the very bulky and oxygenophilic methylaluminum diphenoxides (MAD and MABR), recently intoduced by Yamamoto, are perfectly compatible with radical reactions and provide exceptional levels of stereocontrol (up to 98:2) when used stoichiometrically. A good level of stereoselectivity (90:10) was reached by using a catalytic amount of MABR (10%). The yields and the stereoselectivities of the radical allylations compare favorably with the nucleophilic allylation of the deprotonated tetrahydrothiophene 1-oxide.

Introduction

Lewis acids have recently begun to show promise as additives for altering the stereochemistry of radical addition and cyclization reactions.[1] In one of the earliest studies in this area, Renaud and Ribezzo communicated[1a] that trans-selectivity in the radical allylation of α-phenylseleno sulfoxide **1** with allyl tributylstannane was enhanced by the addition of stoichiometric amounts of traditional Lewis acids like $BF_3{\bullet}Et_2O$ and $ZnCl_2$ (eq 1). In related work, Waldner, De Mesmaeker, and co-workers[2,3] observed increases in stereoselectivity in allylations of α-sulfinyl radicals when reactions were conducted in hydrogen bond donating solvents like 2,2,2-trifluoroethanol. Taken together, these results suggest the intermediacy of complexed (or hydrogen bonded) α-sulfinyl radicals **2**.

We now report full details of an expanded study of the effects of solvents and Lewis acids on the radical allylations of **1**. The starting point of this study was the discovery that the ratios of **3**-trans/**3**-cis reported in the original communication[1a] were too high. We describe herein our studies that determine the origin of the errors, and we also report the corrected ratios. Despite the quantitative errors in product ratios, the original results were qualitatively correct, and the original conclusions stand.



Beyond this, we have discovered that bulky aluminum phenoxide Lewis acids provide exceptional levels (up to 98/2) of stereoselectivity when used stoichiometrically, and good levels of stereoselectivity (up to 90/10) are still observed when these Lewis acids are used catalytically (10 mol %). Finally, we discuss the implications of the results and we suggest possible origins for the yield and selectivity trends that are observed.

Results and Discussion

Determination of the 3-Trans/3-Cis Ratio. Problems with the originally reported ratios of **3**-trans/**3**-cis were revealed when several of these reactions were repeated as standards for the study of the effects of diaryl urea additives on allylations of α-sulfinyl radicals.[4] Table 1, column A, summarizes some of the results originally reported for the allylations of phenylselenide **1** with and without Lewis acids.[1a] In these experiments, ratios of **3**-trans/**3**-cis were determined in Lausanne by GC (packed column, SE 30, 150–200 °C). Repeat experiments were conducted in Pittsburgh, and the trans/cis ratios were determined by integration of appropriate resonances[5] in the ^1H NMR spectrum recorded in C_6D_6 (Table 1, column

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(1) (a) Renaud, P.; Ribezzo, M. *J. Am. Chem. Soc.* **1991**, *113*, 7803–7805. (b) Newcomb, M.; Ha, C. *Tetrahedron Lett.* **1991**, *32*, 6493–6496. (c) Guindon, Y.; Lavallée, J. F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701–9702. (d) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300–3302. (e) Toru, T.; Watanabe, Y.; Tsusaka, M.; Ueno, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10464–10465.

(2) (a) Waldner, A.; De Mesmaeker, A.; Hoffmann, P.; Mindt, T.; Winkler, T. *Synlett* **1991**, 101–103. (b) De Mesmeaker, A.; Waldner, A.; Hoffmann, P.; Mindt, T. *Synlett* **1993**, 871–874.

(3) For stereoselective reactions of α-sulfinyl radicals without additives, see: (a) Snider, B. B.; Wan, B. Y.-F.; Buckman, B. O.; Foxman, B. M. *J. Org. Chem.* **1991**, *56*, 328–334. (b) Beckwith, A. L. J.; Hersperger, R.; White, J. M. *J. Chem. Soc., Chem. Commun.* **1991**, 1151–1152. (c) Renaud, P.; Carrupt, P.-A.; Gerster, M.; Schenk, K. *Tetrahedron Lett.* **1994**, *35*, 1703–1706. (d) Renaud, P.; Bourquard, T. *Tetrahedron Lett.* **1994**, *35*, 1707–1710.

(4) Certain diaryl ureas do enhance trans selectivities in the allylations of **1**, and these studies are being communicated separately: Curran, D. P.; Kuo, L. H. *J. Org. Chem.*, submitted.

(5) Resonances for the **3**-cis and **3**-trans are not adequately resolved in $CHCl_3$, but ratios can be determined by integrating spectra recorded in C_6D_6. See Experimental Section.

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Table 1. Allylations of Phenylseleno Sulfoxide 1.[a] Comparison of 3-trans/3-cis Ratio Obtained by ^{1}H-NMR and GC Analysis

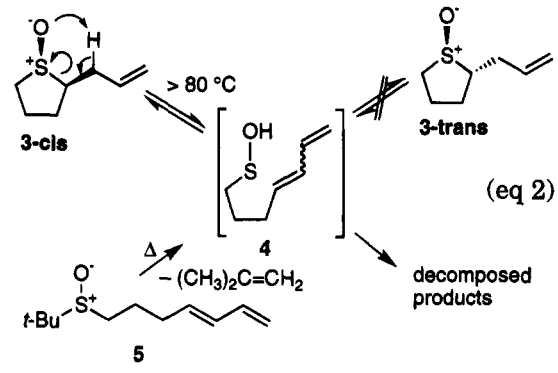
			ratio 3-trans/3-cis (% isolated yield)		
entry	solvent	additive	A[b]	B[c]	C[d]
1	benzene	none	86:14 (72)	70:30 (60)	82:18
2	CH_2Cl_2	none	93:17 (86)	82:18 (62)	–
3	THF	none	87:13 (58)	69:31 (36)	76:24
4	THF	LiCl (0.5 M)	94:6 (25)	84:16 (25)	92:8
5	THF	$ZnBr_2$ (0.5 M)	97:3 (62)	88:12 (60)	93:7
6	THF	BF_3·Et_2O (0.5 M)	98:2 (55)	82:18 (73)	91:9

[a] Sulfoxide 1 [0.4 M], allyltributylstannane [0.5 M], additive, and AIBN were dissolved in the indicated solvent and irradiated for 24 h at 15 °C. [b] Lausanne GC results (ref 1a). [c] This work, Pittsburgh ^{1}H-NMR analysis. [d] This work, Pittsburgh GC analysis.

B). These ^{1}H NMR ratios were significantly lower (typically by a factor of 2–4) than the reported GC ratios. Several of the reactions conducted in Pittsburgh were also analyzed by GC (fused silica capillary column, SPB-1, 80–250 °C), and a third, entirely different series of ratios was obtained (Table 1, column C). These ratios were consistently lower than the Lausanne GC results but consistently higher than the Pittsburgh NMR results.

The results from all three methods of analysis were reproducible, and since there was no reason to question the accuracy of the ratios determined by ^{1}H NMR integration, a systematic error in the GC analyses seemed likely. Though response factors were not determined, we felt it unreasonable that differences in response factors of diastereomers 3-trans and 3-cis could skew the raw GC ratios so much. A more likely origin of the differences between the NMR and GC results might be the thermal sensitivity of 3-cis. At the temperatures of GC injection and separation, 3-cis can be expected to undergo (reversible) syn-elimination of sulfenic acid to give 4 (eq 2). Due to strain in the cyclic transition state, conversion of 3-trans to 4 should be much slower than 3-cis. Since sulfenic acids are well known to be unstable,[6] this suggests a pathway for selective thermal decomposition 3-cis. Control experiments supported this suggestion. The apparent GC of ratio 3-trans/3-cis depends strongly on the conditions of the analysis. On injecting a 2.5/1 mixture into the GC, the apparent trans/cis ratio increased significantly as the column temperature was increased. At fixed column temperatures, the following ratios were recorded for this 71:29 mixture: 110 °C, 87:13; 130 °C, 91:9; 150 °C, 92:8, 170 °C, 94:6; 190 °C, >96:4. On heating a 71:29 mixture of 3-trans/3-cis in benzene containing an integration standard at 80 °C, we observed slow decomposition of 3-cis without discernible change in the amount of 3-trans. After 4 days, most of the starting 3-cis had decomposed. Though the trend was clear, quantitative analysis of this NMR experiment was not possible because the base line region of the ^{1}H NMR spectrum grew quite complex as heating continued.

To prove that 3-cis was decomposing and not isomerizing to 3-trans, we prepared an isomerically pure sample of 3-cis by thermolysis of readily available *tert*-butyl sulfoxide 5 (1.5/1 *Z/E* mixture). Heating of 5 at 110 °C for 24 h effected elimination of isobutene and provided 3-cis in 27% yield. This thermolysis proceeds through the intermediacy of sulfenate ester 4,[7] and as expected for the syn addition, no 3-trans was formed in this experiment. The low yield is presumably due to competing decomposition of the product under the reaction conditions. Heating of pure 3-cis over 4 days at 80 °C again resulted in slow decomposition to products that gave very broad peaks in the ^{1}H NMR spectrum. At no time could we detect any trans isomer. Injection of pure 3-cis into the GC did not give a peak for the trans isomer.



The determination of 3-trans/3-cis ratio by ^{1}H-NMR was corroborated by HPLC measurements (C_{18} reversed phase, H_2O/*i*-PrOH). In all cases, excellent agreement between the HPLC and ^{1}H-NMR analysis was observed. The HPLC method was particularly useful in subsequent experiments when the ratios were higher than 95:5 because of the relative imprecision of the ^{1}H-NMR signal integration at these levels. All ratios reported in the following sections were determined by HPLC analysis.

Solvent Effects. The influence of the solvent was investigated by conducting the allylation of 1 in several solvents (Table 2). In a standard procedure, a solution of 1 (0.4 M), allyltributylstannane (1.25 equiv), and AIBN in the indicated solvent at 10 °C (internal temperature) was irradiated with a 300-W sunlamp for 24 h. After rapid filtration through silica gel, the product ratio was measured by HPLC analysis and the products were purified by flash chromatography to determine isolated yields. Most reactions were performed with a 92:8 ratio of 1-trans/1-cis. Two control experiments with diastereomerically pure 1-cis gave the same diastereoselectivity (entries 1 and 3, results in brackets) as the trans-rich mixture. This supports the existence of the common radical intermediate 2 formed from either isomer of 1.

Solvent effects were modest and variable. In the noncoordinating solvent CH_2Cl_2, a 3-trans/3-cis ratio of 82:18 (entry 1) was observed. A similar result (77:23) was obtained in propiononitrile (entry 2). In benzene and THF, the diastereoselectivity was noticeably lower (70:30 and 69:31, entries 3 and 4). We attribute this lowering to the coordination of the solvent at the sulfoxide sulfur atom anti to the oxygen. This type of coordination is well documented for aromatic solvents.[8] For example, recording ^{1}H-NMR spectra in C_6D_6 has been frequently used to assign the relative configurations of α-substituted cyclic sulfoxides because of the anisotropic shielding caused by the aromatic ring.[9] This analogy suggests the structure 2a for the benzene-coordinated radical intermediate. THF is also expected to coordinate sulfoxides at the sulfur atom

(6) Leading references: (a) Chou, T. S.; Burgtorf, J. R.; Ellis, A. L.; Lammert, S. R.; Kukolja, S. P. *J. Am. Chem. Soc.* **1974**, *96*, 1609–1610. (b) Davis, F. A.; Friedman, A. J. *J. Org. Chem.* **1976**, *41*, 897–898. (c) *The Chemistry of Sulfenic Acids and Their Derivatives*, Patai, S., Ed.; Wiley: Chichester, 1990.

(7) For closely related experiments, see: Jones, N.; Lewton, D. A. *J. Chem. Soc., Chem. Commun.* **1974**, 457–458. Barrett, A. G. M.; Barton, D. H. R.; Nagubandi, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 237–239.

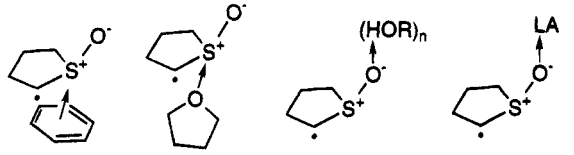
(8) Ledaal, T. *Tetrahedron Lett.* **1968**, 1683–1688.

(9) Lett, R.; Marquet, A. *Tetrahedron* **1974**, *30*, 3379–3392.

Table 2. Allylation of Phenylseleno Sulfoxide 1. Effects of Solvents and Lewis Acidic Additives

entry	solvent	additive	% isolated yield	3-trans/3-cis
1	CH_2Cl_2	–	63 (63)[a]	82:18 (82:18)[a]
2	CH_3CH_2CN	–	88	77:23
3	C_6H_6	–	78 (49)[a]	70:30 (70:30)[a]
4	THF	–	44	69:31
5	EtOH	–	87	83:17
6	TFE	–	83	89:11
7	AcOH	–	51	87:13
8	CH_2Cl_2	$Eu(dpm)_3$	55	89:11
9	CH_2Cl_2	Et_2AlCl	21[b]	77:23
10	CH_2Cl_2	$Ti(Oi\text{-}Pr)_3Cl$	28	86:14
11	CH_2Cl_2	TBAP	88	81:19
12	THF	ZnBr2	58	88:12
13	THF	$BF_3{\cdot}Et_2O$	75	82:18
14	THF	LiCl	29	84:16
15	C_6H_6	*t*-BuCOOH	79	78:22
16	CH_3CH_2CN	$LiClO_4$	84	90:10

[a] Starting from pure 1-cis. [b] Partial reduction of the sulfoxide is occurring.



2a 2b 2c 2d

Figure 1. Possible mode of complexation of the radical intermediate **2**.

because of its Lewis base character (see **2b**). In both cases (**2a** and **2b**), solvent molecules shield the face of preferential attack and reduce the selectivity. In contrast to benzene and THF, protic solvents enhanced the stereoselectivity (entries 5–7).[2] This modest enhancement was greater with 2,2,2-trifluoroethanol (89:11) than with EtOH (83:17) or AcOH (87:13), and it can be attributed to hydrogen bonding with the oxygen atom of the sulfoxide (**2c**).[2]

Effect of Bronsted and Lewis acids. The effects of solvents suggested that complexation at the oxygen atom (**2d**) represented a promising opportunity to enhance the stereoselectivity of the allylation reaction. To investigate the effects of additives potentially able to coordinate sulfoxides, we conducted a series of reactions under the standard conditions in the presence of 1.1 equiv of some representative Bronsted and Lewis acids (Table 2, entries 8–16). Solvents varied according to the additives. To eliminate the possibility that the additives promoted nonradical reactions, we verified that no reaction occurred in any case in the absence of radical initiator and irradiation.

Classical Lewis acids moderately enhance the stereoselectivity. The best result was obtained in CH_2Cl_2 with $Eu(dpm)_3$ (89:11), a lanthanide that is often used as a shift reagent for elucidation of ^{1}H-NMR spectra of sulfoxides.[9] In this case, the isolated yield (55%) was somewhat lower than the yield in the additive-free experiment (entry 1, 63%). With Et_2AlCl and $Ti(Oi\text{-}pr)_3Cl$ as additives (entries 9 and 10), the yields were markedly lower due to side reactions (entry 9) or lowering of the reaction rate (entry 10). Protic acids were not very useful; pivalic acid provided a modest increase in selectivity (entry 15), but an attempt to use trifluoroacetic acid failed since it precluded any radical reaction. A good enhancement of stereoselectivity was obtained with lithium perchlorate in propiononitrile (from 77:33 to 90:10, compare entries 3 and 16). This very mild Lewis acid is particularly interesting because it is completely compatible with radical reactions and it induced no lowering of the yield.[10] The perchlorate counterion has no influence on the stereoselectivity as shown from the reaction in the presence of tetrabutylammonium perchlorate (TBAP) (compare entries 1 and 11). The use of lithium chloride in THF (entry 7) is less efficient than lithium perchlorate in propiononitrile.

Table 3. Allylation of Phenylseleno Sulfoxide 1 in the Presence of methylaluminum Diphenoxides

entry[a]	$MeAl(OAr)_2$ (equiv)	yield	3-trans/3-cis
1	MAP (1.1)	78	93:7
2	MAD (1.1)	72	98.2:1.8
		80[b]	98.6:1.4[b]
		69[c]	98.5:1.5[c]
3	MAD (0.1)	63	85:15
4	MABR (1.1)	57	98.1:1.3
5	MABR (0.1)	66	90:10

[a] 1 mmol scale. [b] mmol scale. [c] Starting from pure cis-1, all other reactions were run with a 1-trans/1-cis 92:8 mixture of diastereoisomers.

The simple model (**2d**) proposed to account for the stereoselectivity enhancement in the presence of Lewis acid is based on steric effects. It was of interest to test the use of very bulky and oxygenophilic Lewis acids such as the methylaluminum phenoxide derivatives introduced by Yamamoto.[11] These unique reagents are useful for a number of reactions such as the cleavage of chiral acetals, nucleophilic addition to ketones, ene reactions, and the generation of a stable complex of formaldehyde.[12] Though Yamamoto's Lewis acids have not been used in radical reactions, it is well known from polymer chemistry that radical reactions can be conducted in the presence of aluminum-based Lewis acids such as aluminum sesquichloride.[13,14]

We have prepared and tested three different methylaluminum diphenoxides, MAP, MAD, and MABR, in order to investigate the influence on stereoselectivity of the size of the phenoxide group (MAP versus MAD) and the influence of the acidity (MAD versus MABR). The aluminum reagents were generated in situ following the procedures of Yamamoto,[12] and then the allylations were conducted as described above. Most reactions were performed with **1** as a 92:8 trans/cis mixture of diastereoisomers (Table 3), but we again verified that pure **1**-cis reacted with the same stereoselectivity as the trans-rich mixture (entry 2).

Very interestingly, the reaction of **1** with allyltributylstannane in CH_2Cl_2 containing 1.1 equiv of MAP was already more selective (Table 3, entry 1, 93:7) than all the traditional Lewis acids that were studied in Table 2. The use of 1.1 equiv of the sterically more bulky MAD gave exceptionally high stereoselectivities of >98:2 coupled with

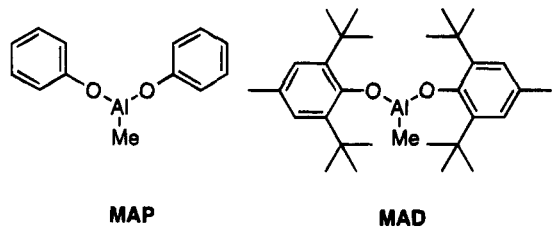
(10) Lithium perchlorate has been recently found to be very efficient for the catalysis of Diels–Alder and 1,4-addition reactions. For a review, see: Grieco, P. *Aldrichim. Acta* **1991**, *24*, 59–66.

(11) Maruoko, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573–4576.

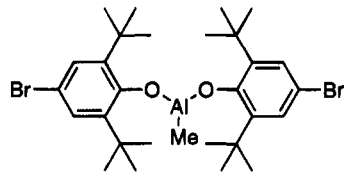
(12) (a) Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 7074–7075. (b) Hirukawa, T.; Shudo, T.; Kato, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 217–225. (c) Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 9011–9013. (d) Maruoka, K.; Concepcion, A. B.; Hirayama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 7422–7423.

(13) (a) Hirooka, M.; Yabuchi, H.; Iseki, J.; Nakai, Y. *J. Polym. Sci. A-1* **1968**, *6*, 1381. (b) Lyons, R. A.; Moad, G.; Senogles, E. *Eur. Polym. J.* **1993**, *29*, 389–395.

(14) Lyons, R. A.; Moad, G.; Senogles, E. *Eur. Polym. J.* **1993**, *29*, 389–395.



MAP MAD

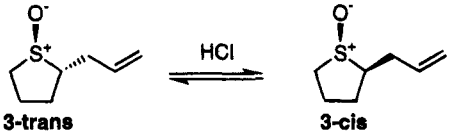


MABR

good yields (entry 2). On a small scale (≤1 mmol), the reaction with MAD occurred in the absence of AIBN, but sunlamp irradiation was necessary. We believe that upon irradiation, the methylaluminum diphenoxides produce methyl radicals which initiate the reaction.[15] On a larger scale (4 mmol), AIBN was necessary for the reaction to go to completion in a reasonable time (<24 h). The use of 1.1 equiv of MABR gave a diastereoselectivity of 98.6:1.4 (entry 4).

We also conducted two experiments with only catalytic quantities of these Lewis acids. While the presence of 10% MAD furnished only a relatively small stereoselectivity enhancement (entry 3, 85:15), the use of a catalytic amount of MABR (10%) gave a selectivity enhancement equal to that of the best traditional Lewis acids used stoichiometrically (entry 3, 90:10). This result may be explained by a rate acceleration of either the radical addition step or the selenium abstraction step caused by the complexation to MABR. An alternative explanation of selectivity enhancement based on aggregate formation does not seem likely with these very hindered reagents.

To elucidate whether the enhancing effects of Lewis acids have kinetic or thermodynamic origins, we conducted a series of control experiments. HCl in organic solvents is well known to efficiently cause racemization[16] or epimerization[17] of sulfoxides. Since such an epimerization could conceivably also occur in the presence of Lewis acids, we first studied the 3-trans/3-cis equilibrium by epimerization of the sulfur center with HCl (eq 3).



3-trans 3-cis (eq 3)

Different mixtures of isomers highly enriched in 3-trans or 3-cis were epimerized with 12 M HCl in dioxane and in propiononitrile. In both solvents, very similar 3-trans/3-cis ratios (25:75) were obtained irrespective of the initial ratio. The greater stability of 3-cis is in line with the work of Johnson,[18] who has reported a similar preference for 2-methyltetrahydrothiophene 1-oxide. Since the cis compound is the minor isomer formed in our reactions, epimerization at the sulfur center cannot be responsible for the very high stereoselectivities we have observed in the presence of Lewis acids. Moreover, diastereoisomeric mixtures of trans-3/cis-3 of different compositions were also treated in organic solvents with the Lewis acids we have tested in Tables 2 and 3. No change of the diastereoisomeric ratio was ever observed, indicating that epimerization is not occurring under our reaction conditions.

Finally, we have investigated the ionic allylation of tetrahydrothiophene 1-oxide. It was of interest to compare the stereoselectivity of the radical allylation reaction with the ionic one. Deprotonation of tetrahydrothiophene 1-oxide at −78 °C with LiHMDS and treatment with allyl bromide gave 3 in 46% yield as a trans/cis 89:11 mixture of isomers. This selectivity is comparable in direction and amplitude to the one we obtained by the radical pathway using $LiClO_4$ as additive (Table 2, entry 16). It is, however, much lower than the one obtained with the bulky methylaluminum diphenoxides. The yields obtained by the radical reactions exceed the ionic version because of the formation of substantial amounts of dialkylated products in this latter case.

Conclusions

We have demonstrated that Lewis acids are promising for the control of the stereoselectivity of reactions of radicals adjacent to sulfoxides. A major potential problem—the incompatibility of Lewis acids with radical chain reactions—is overcome by a judicious choice of the Lewis acid. Mild Lewis acids such as lithium cation and stronger Lewis acids such as methylaluminum diphenoxides are completely compatible with standard radical allylation reactions. Moreover, the methylaluminum diphenoxide additives are of special interest because of their large steric requirement and their great site selectivity. Important possible applications for these bulky Lewis acids lie in the control of the stereoselectivity in acyclic systems,[3,19] and such applications are currently being studied.

Catalysis of radical reactions[1b,20] is especially challenging because radical reactions are already very fast. The observation that catalytic quantities of these Lewis acids can still alter selectivity is especially important. Recently, catalytic amounts of diaryl urea additives have also been found to improve the stereoselectivity in the allylation of 1 to a lesser degree.[4] These discoveries may eventually open a way to the catalysis of related radical reactions.

Experimental Section

General. HPLC: Waters Nova-Pak C_{18}, elution with a H_2O/*i*-PrOH 97:3, 2 mL/min. t_R = 3.6 min (cis-3) and 4.6 min (trans-3). Flash chromatography (FC) and filtration: Merck silica gel 60 (70–230 mesh). Irradiation: sunlamp 300 W placed 5 cm from the flask which was partially immersed in a cooling bath. Determination of the cis-3/trans-3 ratio: ^{1}H-NMR (250–

(15) (a) Kunz and Rück have already reported that irradiation of Me_2AlCl produced methyl radicals which have been used for 1,4-addition to α,β-unsaturated *N*-acylurethane: Kunz, H.; Rück, K. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 694–696. (b) Feldman has reported an annulation procedure where trimethylaluminum enhances the reaction rate by complexation of the radical intermediate and is also presumably playing the role of radical initiator: Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Jean, G. *J. Org. Chem.* **1992**, *57*, 100–110.

(16) Mislow, K.; Simmons, T.; Melillo, J. T.; Ternay, A. L., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 1452–1453.

(17) Johnson, C. R.; McCants, D., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 2935–2936.

(18) Equilibration of 2-methylthiolane 1-oxide in HCl/dioxane gave a cis/trans 76:24 mixture of isomers: Rigau, J. J.; Bacon, C. C.; Johnson, C. R. *J. Org. Chem.* **1970**, *35*, 3655–3657.

(19) Thoma, G.; Curran, D. P.; Geib, S. V.; Giese, B.; Damm, W.; Wetterich, F. *J. Am. Chem. Soc.* **1993**, *115*, 8585–8591.

(20) Singleton, D. A.; Huval, C. C.; Church, K. M.; Priestley, E. S. *Tetrahedron Lett.* **1991**, *32*, 5765–5768.

400 MHz, C_6D_6) δ 5.58 (C=CH, trans-**3**); 5.96 (C=CH, cis-**3**). The relative configuration of **3** was assigned from ^{13}C-NMR spectra by comparison with the reported spectra of *trans*- and *cis*-2-methyltetrahydrothiophene 1-oxide.[21] This assignment was confirmed by the thermolysis of **5**.

***trans*-2-(Phenylselenenyl)tetrahydrothiophene 1-Oxide (1-trans).** A solution of hexamethyldisilazane (28 mL, 134 mmol) in THF (160 mL) was treated with BuLi (84 mL, 134 mmol, 1.6 M in hexane) at −78 °C. Tetrahydrothiophene 1-oxide (7.0 g, 67 mmol) was added at −78 °C, followed after 15 mn by a solution of PhSeSePh (20.9 g, 67 mmol) in THF (70 mL). The reaction mixture was stirred for 30 mn at −78 °C, allowed to warm to rt over 2 h, poured into 10% NH_4Cl, and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. FC (EtOAc/petroleum ether 1:1 and EtOAc/MeOH 95:5) gave **1** (9.7 g, 60%) as a trans/cis 92:8 mixture of diastereoisomers which was used for all the radical reactions described below (exception specified). Recrystallization from Et_2O/heptane at −20 °C gave diastereomerically pure 1-trans as a white solid: mp = 30−33 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.73−7.50 (m, 2 arom H), 7.45−7.20 (m, 3 arom H), 4.40 (m, H-C(2)), 3.25 (m, 1H), 3.10−2.75 (m, 2H), 2.54 (m, 1H), 2.30−2.05 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 134.27 (d), 129.31 (d), 128.52 (d), 127.28 (s), 65.01 (d), 51.86 (t), 31.81 (t), 25.17 (t); IR (film) 2953, 1655, 1578, 1478, 1458, 1438; MS (EI) 260 (2, (M^+)), 183 (4), 157 (16), 129 (3), 103 (66), 77 (29), 71 (100), 57 (62). Anal. Calcd for $C_{10}H_{12}OSSe$ (259.31): C, 46.33; H, 4.67; S, 12.37; Se, 30.46. Found: C, 46.27; H, 4.72; S, 12.33; Se, 30.47.

***cis*-2-(Phenylselenenyl)tetrahydrothiophene 1-Oxide (1-cis).** A solution of **1** (trans/cis 92:8) (2.59 g, 10 mmol) in dry CH_2Cl_2 (35 mL) was treated with triethyloxonium tetrafluoroborate (2.3 g, 12 mmol) and stirred for 1 h at rt.[22] A 1 M NaOH solution (15 mL) was added to the reaction mixture. After 15 mn stirring at rt, the reaction mixture was extracted with CH_2Cl_2. Drying ($MgSO_4$), evaporation of the solvent, and FC (EtOAc) gave **1** (cis/trans 83:17). Diastereomerically pure 1-cis was obtained by recrystallization from Et_2O/hexane (1.6 g, 61% yield) as a white solid: mp = 54−55 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.72−7.69 (m, 2 arom H), 7.39−7.28 (m, 3 arom H), 4.14 (m, H-C(2)), 3.13 (m, 1H), 2.98 (m, 1H), 2.58−2.33 (m, 3H), 1.96 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.53 (d), 129.81 (d), 128.90 (d), 128.50 (s), 66.0 (d), 54.95 (t), 33.11 (t), 25.28 (t); IR (KBr) 2918, 15.71, 1479, 1441; MS (EI) 261 (7, (M^+ + 1)), 260 (2), 259 (3), 183 (3), 157 (16), 129 (3), 116 (13), 103 (90), 77 (32), 71 (100), 57 (40). Anal. Calcd for $C_{10}H_{12}OSSe$ (259.31): C, 46.33; H, 4.67. Found: C, 46.34; H, 4.70.

7-[(*tert*-Butyldimethylsilyl)oxy]-1,3-heptadiene. To a stirred solution of allyltriphenylphosphonium bromide (4.55 g, 11.88 mmol) in tetrahydrofuran (30 mL) was added *n*-butyllithium (6 mL, 2 M in pentane, 11.88 mmol) dropwise at −78 °C. The mixture was stirred at 25 °C for 30 min before being cooled to −78 °C. A solution of 4-[(*tert*-butyldimethylsilyl)oxy]butanal (1.60 g, 7.92 mmol) in tetrahydrofuran (30 mL) was added dropwise. The reaction mixture was allowed to stir at 25 °C for 1 h. Water (100 mL) was added and the mixture was extracted with ether (2 × 100 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), and dried over magnesium sulfate. Purification by flash column chromatography (hexanes/EtOAc = 100/1) yielded the silylated diene as a colorless liquid containing cis and trans isomers in 1.5/1 ratio (0.93 g; 52%): ^{1}H NMR ($CDCl_3$) δ [6.75−6.58 (m, minor isomer), 6.39−6.23 (m, major isomer), totaling 1 H], 6.14−5.96 (1 H, m), [5.76−5.68 (m, major isomer), 5.53−5.39 (m, minor isomer), totaling 1 H], 5.24−4.92 (2 H, m), 3.61 (2 H, t, J = 6.4 Hz), [2.45−2.23 (m, minor isomer), 2.22−2.09 (m, major isomer), totaling 2 H], 1.76−1.55 (2 H, m), 0.95 (9 H, s), 0.04 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 137.3, 134.9, 132.3 (2 lines), 131.2, 129.6, 116.9, 114.8, 62.5, 62.4, 32.7, 32.3, 28.9, 26.0 (2 C), 24.1, 18.4 (2 C), −5.2 (2 C); IR (thin film) 2932, 2858, 1471, 1255, 1103 cm^{-1}; MS, *m*/*z* 211 ($M^+ - CH_3$), 169 ($M^+ - {}^tC_4H_9$), 141, 101, 75.

7-Bromo-1,3-heptadiene. To a stirred solution of the above silyl ether (0.87 g, 3.85 mmol) in methylene chloride (11 mL) at 25 °C was added a solution of dibromotriphenylphosphorane (1.79 g, 4.23 mmol) in methylene chloride (11 mL). After 5 h the reaction mixture was diluted with water (30 mL) and the mixture was extracted with methylene chloride (2 × 30 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL) and dried over magnesium sulfate. Purification by flash column chromatography (hexanes/EtOAc = 100/1) yielded the bromo diene as a colorless liquid (0.46 g; 69%): ^{1}H NMR ($CDCl_3$) δ [6.73−6.60 (m, minor isomer), 6.37−6.25 (m, major isomer), totaling 1 H], 6.15−6.04 (1 H, m), [5.70−5.60 (m, major isomer), 5.45−5.36 (m, minor isomer), totaling 1 H], 5.25−4.99 (2 H, m), 3.42 (2 H, t, J = 6.6 Hz), [2.36 (q, J = 7.1 Hz, minor isomer), 2.25 (q, J = 6.9 Hz, major isomer), totaling 2 H], 1.96 (2 H, quint, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 136.8, 132.7, 132.3, 131.9, 130.7, 130.1, 117.7, 115.6, 33.2 (2 C), 32.4, 32.0, 30.8, 26.1; IR (thin film) 2945, 2355, 2330, 1030 cm^{-1}.

***tert*-Butyl 4,6-Heptadienyl Sulfide.** To a suspension of sodium hydride (86.4 mg, 3.60 mmol) in tetrahydrofuran (10 mL) was added dropwise a solution of 2-methyl-2-propanethiol (0.22 g, 2.40 mmol) in tetrahydrofuran (5 mL) at 0 °C over 10 min. The suspension was stirred at 25 °C for 1 h before being cooled to 0 °C. A solution of the above bromo diene (0.42 g, 2.40 mmol) in tetrahydrofuran (5 mL) was added dropwise at 0 °C over 10 min. The reaction mixture was allowed to stir at 25 °C for 4 h. Water (10 mL) was added and the mixture was extracted with ether (2 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL) and dried over magnesium sulfate. Purification by flash column chromatography (hexanes/EtOAc = 40/1) yielded sulfide **6** as a colorless liquid (0.40 g; 91%): ^{1}H NMR ($CDCl_3$) δ [6.72−6.60 (m, minor isomer), 6.38−6.25 (m, major isomer), totaling 1 H], 6.13−6.00 (1 H, m), [5.73−5.64 (m, major isomer), 5.48−5.40 (m, minor isomer), totaling 1 H], 5.22−4.96 (2 H, m), 2.56−2.51 (2 H, m), [2.31 (q, J = 7.4 Hz, minor isomer), 2.20 (q, J = 7.2 Hz, major isomer), totaling 2 H], 1.73−1.63 (2 H, m), 1.32 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 137.1, 134.0, 132.2, 131.6, 131.5, 130.0, 117.1, 115.1, 41.9 (2 lines), 31.9, 31.0 (2 lines), 30.5, 29.6, 29.3, 27.7, 27.1; IR (thin film) 2957, 1651, 1458, 1363, 1163 cm^{-1}.

***tert*-Butyl 4,6-Heptadienyl Sulfoxide (5).** To a stirred solution of the above sulfide (0.10 g, 0.54 mmol) in ethanol (8.5 mL) was added dropwise a solution of sodium periodate (0.12 g, 0.57 mmol) in water (3 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 20 h. Water (10 mL) was added and the mixture was extracted with methylene chloride (2 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL) and dried over magnesium sulfate. Purification by flash column chromatography (hexanes/EtOAc = 1/100) yielded sulfoxide **5** as a pale yellow liquid (65.2 mg; 60%): ^{1}H NMR ($CDCl_3$) δ [6.67−6.54 (m, minor isomer), 6.36−6.23 (m, major isomer), totaling 1 H], 6.12−6.02 (1 H, m), [5.70−5.61 (m, major isomer), 5.46−5.37 (m, minor isomer), totaling 1 H], 5.23−4.97 (2 H, m), 2.53−2.43 (2 H, m), 2.42−2.24 (2 H, m), 2.03−1.84 (2 H, m), 1.23 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 136.7, 132.9, 132.2, 131.7, 130.5, 130.4, 117.6, 115.5, 52.6 (2 lines), 44.7, 44.5, 31.4, 26.5, 23.3, 23.0, 22.7 (2 lines); IR (thin film) 2965, 2866, 1460, 1363, 1043 cm^{-1}.

***cis*-2-Allyltetrahydrothiophene 1-Oxide (3-cis).** To an NMR tube was added heptadienyl sulfoxide **5** (53.0 mg, 0.26 mmol) in benzene (0.65 mL). The tube was then sealed and heated at 110 °C for 24 h. Purification by flash column chromatography (EtOAc/MeoH = 25/1) yielded allyl sulfoxide **3-cis** as a pale yellow liquid (10.4 mg; 27%). The product was identical to a sample prepared by the allylation procedure described below.

2-Allyltetrahydrothiophene 1-Oxide (3). Anionic allylation. A solution of LiHMDS (95.9 mmol) in THF (137 mL) was added at −78 °C to a solution of tetrahydrothiophene 1-oxide (10 g, 96 mmol) in THF (200 mL), followed after 15 mn by allyl bromide (9.74 mL, 115.2 mmol). The reaction mixture was allow to warm to rt overnight and poured into 10% NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. FC

(21) Barbarella, G.; Rossini, S.; Bongini, A.; Tugnoli, V. *Tetrahedron* **1985**, *41*, 5691−4701.
(22) Johnson, C. *J. Am. Chem. Soc.* **1963**, *85*, 1020−1021.

(EtOAc, EtOAc/MeOH 95:5 and 10:1) gave **3** (6.4 g, 46% yield) as a trans/cis 89:11 mixture of isomers. Colorless liquid.

Radical Allylation. Method A (solvent effect): A solution of **1** (0.52 g, 2.0 mmol), allyltributylstannane (0.93 mL, 2.5 mmol), and AIBN (15 mg) in the solvent (5 mL) was irradiated for 24 h at 10 °C with addition of AIBN every 8 h. Concentration and filtration through a short column of silica gel (EtOAc/petroleum ether 1:1 for the elution of the nonpolar material and EtOAc/MeOH 80:20 for the elution of **3** gave crude **3** as an inseparable mixture of isomers which was analyzed by ^{1}H-NMR and HPLC for trans/cis ratio. Pure **3** was obtained by FC (EtOAc/MeOH 95:5).

Method B (effect of additives): A solution of **1** (0.52 g, 2.0 mmol), additive (2.2 mmol), allyltributylstannane (0.93 mL, 2.5 mmol), and AIBN (15 mg) in solvent (5 mL) was irradiated for 24 h at 10 °C. AIBN was added every 8 h. (a) In the BF_3/Et_2O case, pyridine (2 mL) was added and the product was poured into water and extracted with CH_2Cl_2. (b) In the case of Et_2AlCl and Ti derivatives, solid $Na_2CO_3{\cdot}10H_2O$ was added to the reaction mixture. After 1 h stirring at rt, the reaction mixture was filtered through Celite. (c) In all other cases, no special treatment was applied. Finally the organic phases were treated as in method A.

Method C (effect of $MeAl(OAr)_2$). Small scale: To a solution of ArOH (2.2 mmol) in CH_2Cl_2 (1.1 mL) was added at rt a 2 M solution of Me_3Al (0.55 mL, 1.1 mmol) in heptane. The methane gas evolved immediately. After stirring at room temperature for 1 h, a solution of **1** (0.26 g, 1.0 mmol) in CH_2Cl_2 (0.85 mL) was added followed by allyltributylstannane (0.46 mL, 1.25 mmol). The reaction mixture was irradiated for 24 h at 10 °C and diluted with CH_2Cl_2 (20 mL). A solution of 1 N NaOH (5 mL) was added and the mixture was stirred for 15 mn and extracted with CH_2Cl_2. The residue obtained after drying ($MgSO_4$) and concentration was treated as in Method A. Large scale: From 2,6-di-*tert*-butyl-4-methylphenol (1.94 g, 8.8 mmol) in CH_2Cl_2 (5 mL), Me_3Al (2.2 mL, 4.4 mmol), **1** (1.04 g, 4.0 mmol), and AIBN (30 mg) under similar reaction conditions as above. The reaction gave **3** as a trans/cis 98.6:1.4 mixture of diastereoisomers (0.46 g, 80%).

Conversion of 3-trans to 3-cis.[22] A solution of **3**-trans/**3**-cis (89:10, 2.0 g, 13.9 mmol) in dry CH_2Cl_2 (50 mL) was treated with Et_3OBF_4 (3.2 g, 17 mmol) and stirred for 1 h at rt. A 1 M NaOH solution (21 mL) was added to the reaction mixture. After 15 mn stirring at rt, the reaction mixture was extracted with CH_2Cl_2. Drying ($MgSO_4$), evaporation of the solvent, and FC (EtOAc/MeOH 95:5) gave **2**-cis/**3**-trans (86:14, 1.30 g, 65% yield): yellow liquid.

Procedure for Equilibration.[17] A solution of **3** (0.29 g, 2.0 mmol) in dioxane or propiononitrile (12 mL) was treated with 12 M HCl (6 mL) and stirred at rt for 1 h. The reaction mixture was neutralized with 3 N NaOH, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated to give crude epimerized **2** which was analyzed for its cis/trans content. Further purification by FC (EtOAc/MeOH 95:5) gave pure **2** (0.29 g, quantitative). Initial ratio: (a) 89:11, (b) 19:81, (c) 89:11; solvent: (a) dioxane, (b) dioxane, (c) propiononitrile; final ratio (a) 25:75, (b) 24:76, (c) 25:75.

3-trans: ^{1}H NMR (400 MHz, C_6D_6) δ 5.58 (m, C=CH), 5.05–4.95 (m, C=CH_2), 2.88 (m, 1H), 2.55 (m, 1H), 2.20–1.95 (m, 4H), 1.75 (m, 1H), 1.55 (m, 1H), 1.04 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 133.90 (d), 117.93 (t), 70.20 (d), 52.62 (t), 34.22 (t), 31.18 (t), 25.03 (t); IR (film) 2980, 2940, 16.40, 1440, 1410. MS (EI) 144 (5, (M^+)), 127 (50), 103 (16), 95 (51), 93 (20), 81 (41), 79 (62), 67 (100), 63 (48), 55(56), 53 (42). **3**-cis: ^{1}H NMR (200 MHz, C_6D_6) δ 5.96 (m, C=CH), 5.40–5.15 (m, C=CH_2), 2.86 (m, 1H), 2.66–2.29 (m, 3H), 2.27–1.85 (m, 3H), 1.68 (m, 1H), 1.35 (m, 1H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 134.9, 117.2, 63.8, 54.0, 30.7, 30.1, 24.4; IR (film) 2948, 1641, 1441. Anal. Calcd for $C_7H_{12}OS$ (144.23): C, 58.29; H, 8.39. Found: C, 58.13; H, 8.41.

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