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Design of Sulfides with a Locked Conformation as Promoters of Catalytic and Asymmetric Sulfonium Ylide Epoxidation

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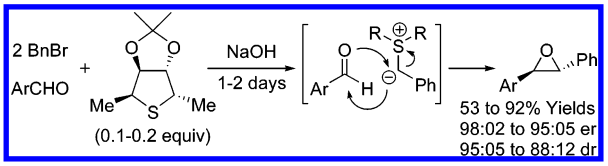
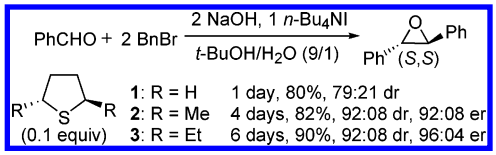


A new generation of 2,5-dimethylthiolanes with a locked conformation was developed to promote the asymmetric addition of chiral sulfonium ylides to aldehydes. The novel chiral sulfur derivative **4** succeeded the synthesis of *trans*-stilbene oxide derivatives with enantiomeric ratios ranging from 95:5 to 98:2. This user-friendly organocatalytic process proved to be efficient with 20−10% of sulfide **4** in 1 or 2 days of reaction. An insight into the ylide intermediate conformation is given on the basis of a computational ab initio study.

The catalytic asymmetric addition of chiral sulfonium ylides to aldehydes has emerged as an efficient approach toward nonracemic epoxides (Scheme 1).[1] The oxirane ring is constructed in a one-step process via a C−C and a C−O bond formation, along which a subtle control of both diastereo- and enantioselectivities is involved.[2] Although the synthesis of nonracemic aromatic epoxide intermediates making use of this ylide methodology has met with some successful elaboration of biologically important targets,[1,3,5a] the number of chiral sulfur derivatives[4] reaching at least 95:5 er in a catalytic approach[5] is thus far limited.[1,2b,6] Aggarwal et al. described a bridged bicyclic sulfide yielding *trans*-stilbene oxide as model substrate with 97:03 er.[6a] An elegant catalytic cycle based on the sulfonium ylide formation by means of rhodium-mediated carbenoid transfer led to a reaction completed within a day with only 0.2−0.05 equiv of sulfide on a large range of aldehyde precursors. On the other hand, Furukawa et al. originally developed in 1989

SCHEME 1. C_2-Symmetrical Thiolanes as Asymmetric Mediators



a transition-metal-free one-pot protocol.[7] This user-friendly and economically reliable method is based on the deprotonation in the presence of a mineral base of the in situ formed nonracemic sulfonium salt from benzyl bromide. In this context, Goodman et al. have recently showed that a readily available C_2 symmetrical sulfide[8] allowed the reaction to reach up to 99:01 er.[6b] Unfortunately, a slow reaction rate usually occured with such a protocol, and a sluggish sulfonium salt formation is often invoked.[9]

Our group developed simple and readily available C_2-symmetric 2,5-disubstituted thiolanes[10] easily used in open reaction vessel (Scheme 1). These sulfonium ylide mediators[11] effected the bis-arylepoxide formation on the order of days.[6c] The *trans*-stilbene oxide was then obtained with up to 96:04 er by means of 0.1 equiv of the diethylthiolane derivative **3**. However, as one can expect, the improved selectivities with the sterically more hindered sulfide **3** led to longer reaction times (**1** vs **2** and **2** vs **3**).

In this paper, we disclose a second generation of C_2 symmetrical thiolanes featuring a controlled topology with the aim to improve the efficiency of this process (Scheme 2). The presence of an acetal bridge at the 3,4 positions of the derivatives **4** and **5** constrains the five-

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(1) For a recent review, see: Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *8*, 611−620.

(2) For recent contributions on getting insight in the reaction mechanisms, see: (a) Silva, M. A.; Bellenie, B. R.; Goodman, J. M. *Org. Lett.* **2004**, *6*, 2559−2562. (b) Aggarwal, V. K.; Richardson, J. *Chem. Commun.* **2003**, 2644−2651. (c) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747−5756.

(3) (a) Aggarwal, V. K.; Imhyuck, B.; Leeb, H.-Y. *Tetrahedron* **2004**, *60*, 9725. (b) Lupattelli, P.; Bonini, C.; Caruso, L.; Gambacorta, A. *J. Org. Chem.* **2003**, *68*, 3360−3362. (c) Solladié-Cavallo, A.; Diep-Vohuule, A. *J. Org. Chem.* **1995**, *60*, 3494−3498.

(4) For recent chiral sulfur reagents promoting bis-arylepoxides synthesis, see: (a) Minière, S.; Reboul, V.; Metzner, P.; Fochi, M.; Bonini, B. F. *Tetrahedron: Asymmetry* **2004**, *15*, 3275−3280. (b) Saito, T.; Akiba, D.; Sakairi, M.; Ishikawa, K.; Otani, T. *Arkivoc* **2004**, *(ii)*, 152−171. (c) Ishizaki, M.; Hoshino, O. *Chirality* **2003**, *15*, 300−305. (d) Aggarwal, V. K.; Angelaud, R.; Bihan, D.; Blackburn, P.; Fieldhouse, R.; Fonquerna, S. J.; Ford, G. D.; Hynd, G.; Jones, E.; Jones, R. V. H.; Jubault, P.; Palmer, M. J.; Ratcliffe, P. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2604−2622. This last reference describes an impressive piece of work toward the elaboration of chiral sulfur derivatives.

(5) For efficient stoichiometric approaches as alternatives, see: (a) Aggarwal, V. K.; Bae, I.; Lee, H.-Y.; Richardson, J.; Williams, D. T. *Angew. Chem., Int. Ed.* **2003**, *43*, 3274−3278. (b) Solladié-Cavallo, A.; Roje, M.; Isarno, T.; Sunjic, V.; Vinkovic, V. *Eur. J. Org. Chem.* **2000**, 1077−1080.

(6) (a) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926−10940. (b) Winn, C. L.; Bellenie, B. R.; Goodman, J. M. *Tetrahedron Lett.* **2002**, *43*, 5427−5430. (c) Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem.* **2001**, *66*, 5620−5623.

(7) Furukawa, N.; Sugihara, Y.; Fujihara, H. *J. Org. Chem.* **1989**, *54*, 4222−4224.

(8) For early attempts to use C_2-symmetrical sulfides, see: Breau, L.; Ogilvie, W. W.; Durst, T. *Tetrahedron Lett.* **1990**, *31*, 35−38. For an intramolecular version: Kim, H.-H.; Metobo, S.; Jimenez, L. S. *Phosphorus, Sulfur, Silicon* **2001**, *176*, 29−47.

(9) A lack of reactivity of the sulfur derivatives, due to the presence electron-withdrawing groups nearby, can also be detrimental to the reaction rate; see: Durst, T. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *74*, 215−232.

(10) 2,5-Dialkylthiolanes are synthesized in two steps from the commercially available chiral 1,4-diols, which are available in bulk from JFC−Juelich Fine Chemicals GmbH Co.: Haberland, J.; Hummel, W.; Daussmann, T.; Liese, A. *Org. Proc. Res. Dev.* **2002**, *6*, 458−462.

(11) A recent review on organocatalysis including sulfur ylides, see: Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175.

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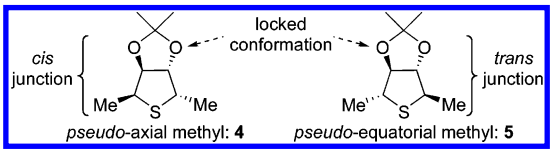
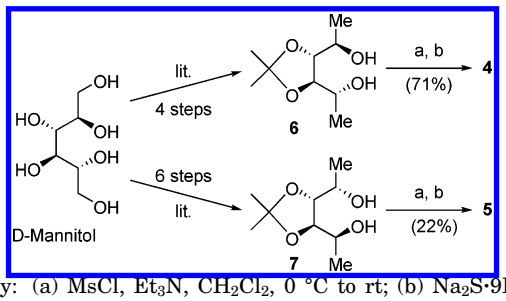
SCHEME 2. C_2-Symmetrical Thiolanes with a Locked Conformation



SCHEME 3. Synthesis of the Chiral Thiolanes[a]



[a] Key: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt; (b) $Na_2S{\cdot}9H_2O$ (4 equiv), DMSO, 50 °C.

membered-ring conformation. Interestingly, the two methyl groups of **4** and **5** are fixed in a different position with respect to the *trans* or the *cis* relationship with the acetal moiety. The 3D-models revealed, on one hand, that the methyl groups of **4** occupy a pseudo-axial position. With structure **5**, these CH_3 groups are forced in a pseudo-equatorial position. The impact upon selectivities would stem from a conformational control of the ring backbone instead of steric hindrance as with 2,5-diethylthiolane **3**.[12] It is expected that maintaining the methyl groups at the C2 and C5 positions would both minimize the shielding of the sulfur lone pair and keep a reasonably rapid rate for the formation of the sulfonium salt. We wish to describe herein the success of such an approach.

The synthesis of new sulfides **4** and **5** was envisaged via diols **6** and **7** (Scheme 3), which were easily obtained in few steps from cheap D-mannitol according to literature procedures.[13] The cyclization step of the known mesylates[14] of **6** and **7** required an excess of sodium sulfide nonahydrate under optimized conditions (see the Supporting Information). The sulfide **4** was thus formed smoothly, in 71% isolated yield over two steps, as a colorless and heavy oil. Under similar conditions, however, the mesylated diol **7** yielded a mixture of products requiring tedious purifications on column chromatography to isolate the sulfide **5** in poor yield. It is believed that the difficult intramolecular substitution reaction by sodium sulfide illustrates the ring strain dictated by the acetal bridge.

Then, we carried out the model synthesis of *trans*-stilbene oxide from benzaldehyde promoted by a catalytic amount of the previous **2** and the new C_2 symmetrical thiolanes **4** and **5** in polar solvents (see the Supporting Information for optimization).[6c] The in situ formation of the sulfonium ylide was performed in the presence of benzyl bromide, a mineral base, i.e., NaOH and the help of an ammonium salt (vide infra). This one-pot protocol is simply performed without exclusion of air or humidity. Under these conditions, an efficient organocatalysis took place with only 0.2 equiv of **4**, leading to 100% conversion in 24 h (Table 1, entry 3). Pleasingly, we measured a high enantiomeric ratio of 98:02 for the formed oxirane in 88% isolated yield. This result constitutes a marked improvement in comparison with the previous generation of dimethylthiolane **2**, which afforded a 92.5:7.5 ratio in favor of the *S*,*S* epoxide (entry 1). Although an erosion of the diastereoselectivity could be observed in protic solvents (entries 1 and 3), the use of acetonitrile allowed us to obtain a 90:10 *trans*/*cis* ratio with a slight decrease of the enantiomeric purity of the oxirane (entries 3 and 4).[2c] Moreover, the configurationally locked sulfide **4** succeeded in the epoxide formation somewhat faster than the flexible thiolane **2** (entries 1−4). The transformation can be completed within 24 h in a catalytic manner. It is worth mentioning that usually several days of reaction are required for such a protocol.[15] Those results place the sulfide **4** as one of the most effective promoter used so far in sulfonium ylide epoxidation.[1] To pursue the study of the remote acetal bridge effects, we carried on the same reaction with the sulfide **5** featuring a *trans* relationship between methyl and ether groups. Whatever the condition A or B (entries 5 and 6), both selectivities and conversions were decreased. The thiolane **5** gave the oxirane enantiomer of the one obtained with **4**, i.e., the major *S*,*S* enantiomer. This demonstrates that the methyl groups at the 2 and 5 positions control the sense of the enantioselectivity.[8]

Moving a step forward to other aldehydes, we were struck by the behavior of the new chiral sulfide **4**. First of all, reproducible results in *tert*-butyl alcohol were obtained for the synthesis of stilbene oxide only with the

TABLE 1. Stilbene Oxide Synthesis with Various C_2-Symmetrical Chiral Thiolanes

entry	thiolane (20%)	cond[a]	time (h)	conv[b] (%)	yield[c] (%)	dr[d] (trans/cis)	er[e] (*S*,*S*/*R*,*R*)
1	**2**	A	48[f]	100	80	90:10	92.5:7.5[g]
2	**2**	B	24	69	62	91:9	91.5:8.5
3	**4**	A	24	100	88	83:17	2:98
4	**4**	B	24	92	75	90:10	5:95
5	**5**	A	168	<20		80:20	nd
6	**5**	B	96	52	27	82:18	74.5:25.5

[a] Conditions A: The reaction mixture of benzaldehyde (1 equiv), benzyl bromide (2 equiv), NaOH (2 equiv), n-Bu_4NI (1 equiv), catechol (0,005 equiv) in a mixture of t-BuOH/H_2O (9/1) was stirred at rt. Conditions B: the reaction mixture of with benzaldehyde (1 equiv), benzyl bromide (2 equiv), n-Bu_4NHSO_4 (0.2 equiv), and NaOH (2 equiv) in a mixture of MeCN/H_2O (9/1) was stirred at rt. [b] Determined by ^{1}H NMR of the crude product with respect to the aldehyde. [c] Isolated yield after column chromatography. [d] Determined by ^{1}H NMR of the crude product. [e] Determined by enantioselective HPLC. [f] A conversion of 86% was measured after 24 h. [g] Our previous results with conditions A without catechol additive, ref 6c.

(12) For computer-assisted modelisation of chiral sulfur reagents, see: (a) Aggarwal, V. K.; Charmant, J. P. H.; Dudin, L.; Porcelloni, M.; Richardson, J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5467−5471. (b) Myllymäki, V. T.; Lindvall, M. K.; Koskinen, A. M. P. *Tetrahedron* **2001**, *57*, 4629−4635. The described chiral sulfide, in this latter paper, allowed the synthesis of *trans*-stilbene oxide with 95:5 er, but in poor yield.

(13) For an excellent review on chiral phospholanes describing the use of diol precursors, see: Clark, P. C.; Landis, C. R. *Tetrahedron: Asymmetry* **2004**, *15*, 2123-2137.

(14) (a) Yan, Y.-Y.; RajanBabu, T. V. *J. Org. Chem.* **2000**, *65*, 900−906. (b) Li, W.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 5871−5874.

(15) Dai already described that 20% of a camphor-derived sulfide allowed stilbene oxide synthesis within a day without the need of any transition metal but a maximum of 80:20 er was obtained; see: Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Huang, Y.-Z.; Li, F.-W. *J. Org. Chem.* **1996**, *61*, 489−493.

TABLE 2. Additive Effects upon Ylide Addition to 4-chlorobenzaldehyde after 24 h[a]

entry	*n*-Bu_4NX X	*n*-Bu_4NX (equiv)	solvent (90/10)	conv (%)	yield (%)	dr (trans/cis)	er (*S*,*S*/*R*,*R*)
1	I[b]	(1)	*t*-BuOH/H_2O	27	15	83:17	5:95
2	I[b]	(1)	MeCN/H_2O	30		84:16	nd
3	I[b]	(0.2)	*t*-BuOH/H_2O	4		nd	nd
4	Br	(0.2)	*t*-BuOH/H_2O	6		nd	nd
5	HSO_4	(0.2)	*t*-BuOH/H_2O	45	38	81:19	4:96
6	HSO_4	(0.2)	MeCN/H_2O	100	71	89:11	5:95
7	HSO_4	(0.2)[c]	MeCN/H_2O	79	64	90:10	4:96

[a] The reaction mixture of aldehyde (1 equiv), benzyl bromide (2 equiv), NaOH (2 equiv) and the sulfide **4** (0.2 equiv) was stirred at rt for 24 h. [b] 0,5% of catechol was used with respect to the aldehyde. [c] 0.1 equiv of sulfide **4** was used.

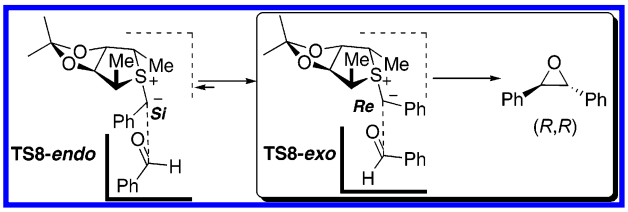
presence of both a small amount of catechol and 1 equivalent of *n*-Bu_4NI.[6c] Next, even though this procedure proved to be robust for benzaldehyde itself, it turned out to be chemically aldehyde dependent.[16] For instance, *p*-chlorobenzaldehyde (Table 2) furnished the corresponding enantioenriched oxirane in 95:5 er, but with only 15% yield after 24 h (entry 1). No improvement was obtained in acetonitrile (entry 2), the alternative polar solvent for this reaction.[17] Then, we undertook an investigation of ammonium additives with 0.2 equiv of sulfide **4** and found a beneficial effect of the counteranion (Table 2). As expected, decreasing the amount of *n*-Bu_4NI to 20% slowed dramatically the reaction rate probably by decreasing the I−Br exchange rate (entry 3). No effect was observed with *n*-Bu_4NBr (entry 4). However, the use of bisulfate as counterion showed an acceleration of the reaction rate in *tert*-butyl alcohol (entry 5). Eventually, the reaction was smoothly performed in acetonitrile in 24 h with only 20% of *n*-Bu_4NHSO_4 (entry 6) and afforded good selectivities for the *trans*-epoxide (without the need of catechol as additive). Furthermore, the loading of the sulfide could be reduced to 0.1 equiv, giving rise to a respectable conversion of 79% (entry 7, 64% yield) after 24 h of reaction without decreasing the selectivity. It is worthy of note that these conditions also provided good reaction rates with dimethylthiolane derivative **2** in acetonitrile (Table 1, entry 2). Although the effect of this ammonium salt is not clear at the moment, we suppose that it behaves as a phase transfer catalyst[18] in this heterogeneous mixture.[19] It would support both the extraction of the hydroxide anion into the organic phase and/or the deprotonation of the sulfonium salt. In fact,

TABLE 3. Asymmetric Synthesis of Epoxides from Various Aldehydes

entry	ArCHO	cond[a]	conv (%)	yield (%)	dr (trans/cis)	er (*S*,*S*/*R*,*R*)
1	2-NaphthylCHO	A	100	92	83:17	4:96
2	2-NaphthylCHO	B	72	65	92:8	5:95
3	4-$F_3CC_6H_4CHO$	A	100	58	90:10	5:95
4	4-$F_3CC_6H_4CHO$	B	100	53	95:5	4.5:95.5
5	4-FC_6H_4CHO	B	100	61	88:12	5:95
6	4-MeC_6H_4CHO	B	84[b,c]	66	90:10	2.5:97.5

[a] Refer to condition A or B of Table 1. [b] Result after 48 h of reaction. [c] Conversion of 46% after 24 h.

SCHEME 4. Asymmetric Induction with the Locked Chiral Sulfide 8



we were able to check by ^1H NMR that the formation of the sulfonium salt between 2 equiv of benzyl bromide and 1 equiv of sulfide **4** in a mixture of CD_3CN/D_2O (9/1)[20] is nicely completed within 3 h.[4a] The subsequent addition of 2 equiv of NaOD and benzaldehyde revealed a slow formation of the epoxide even after several days without any other additives. This first experiment points out that the ylide formation or the ylide addition to the aldehyde seems to be sluggish for the corresponding sulfide **4** in the absence of an ammonium salt.

Having established robust experimental conditions for an enantioselective addition of sulfur ylide to aldehyde with 0.2 equiv of the thiolane **4**, we were interested in probing the generality of this process with a set of para-substituted aromatic aldehydes and 2-naphthaldehyde (Table 3). In almost all cases a complete conversion was obtained after 24 h with moderate to good yields. We were able to measure excellent levels of selectivity for the major *trans*-oxirane (at least 95:05 er). In the case of tolualdehyde (entry 6) a slower reaction rate required 2 days of reaction but a high enantiomeric ratio of 97.5:2.5 was obtained. In general, the diastereoselectivity[2c] was better in acetonitrile than in *t*-BuOH (entries 1−4) without affecting the enantioselectivity. Those results bring confidence to the usefulness of such a constrained C_2-symmetrical 2,5-dimethylthiolane structure **4**.

It is now well recognized[2] that ylide reagent intermediates would adopt two conformations featuring a minimum of energy, i.e., *exo* and *endo* conformations, as seen in Scheme 4 (ylide **8** from sulfide **4** as an exemple), so that the filled p orbital of the sp^2-hybridized ylide carbon is perpendicular to the sulfur lone pair in order to minimize the electronic repulsions. The incoming aryl-aldehyde would then approach the ylide moiety following a cisoid or gauche addition (Scheme 4).[2c] A very recent theorical study by Goodman,[2a] at the DFT level with C_2-

(16) It was found that a complete and reproducible conversion occurred in 24 h when distilled benzaldehyde was stabilized with a small amount of catechol. Although catechol is a well-known antioxidant of aldehydes, such behavior in our process is not completely understood. Moreover, this effect was aldehyde dependent. For instance, no difference was observed with 2-naphthaldehyde whatever catechol was used or not.

(17) Julienne, K.; Metzner, P.; Henryon, V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 731−735.

(18) *n*-Bu_4NHSO_4 has been used as PTC for sulfur ylide epoxidation in a racemic approach, see: Solladié-Cavallo, A.; Lupattelli, P.; Marsol, C.; Isarno, T.; Bonini, C.; Caruso, L.; Maiorella, A. *Eur. J. Org. Chem.* **2002**, 1439−1444.

(19) The ability of HSO_4^- or SO_4^{2-}, in basic conditions, to perform a counterion exchange with the sulfonium bromide cannot be ruled out, as has been also suggested by a reviewer. This exchange would promote the nonreversible formation of the sulfonium salt due to the non-nucleophilic caracter of the sulfate anions. The ammonium ion would facilitate the sulfate anion extraction from the aqueous phase.

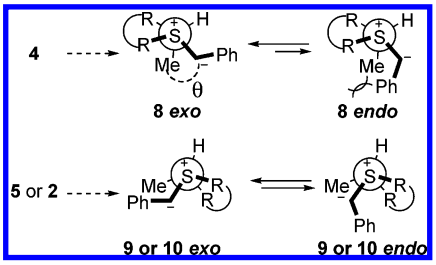
(20) This equilibrium proved to be finely balanced with regard to the solvent polarity. In pure CD_3CN without D_2O, we did not observe any sulfonium salt formation by ^1H NMR even after 24 h; see the Supporting Information.

TABLE 4. Ab Initio Computational Studies on Sulfur Ylides 8−10

entry	benzylidene ylides[a]	corresponding sulfide	$\Delta E_{endo-exo}$ (kJ/mol)[a]	θ_{endo}[b,c] (deg)	θ_{exo}[b,c] (deg)
1	**8**	**4**	3.54	+20.1	+11.6
2	**9**	**5**	1.62	+13.9	+24.8
3	**10**	**2**	0.99	+17.0	+25.5

[a] Exo or endo conformation as described in Scheme 5 and see comment in ref 21. [b] Dihedral angle measured between the carbon atom of the methyl group at the α position of the sulfur atom and the ylide carbon atom. [c] A positive sign means a counterclockwise rotation of the dihedral angle.

SCHEME 5. Conformation of the Ylide Intermediates from ab Initio Calculation



symmetrical thiolanes such as **2**, revealed that the enantioselectivy of the *trans*-epoxide is controlled in the transition state of this carbon−carbon bond formation step (**TS8-*exo*** vs **TS8-*endo***). Accordingly, we assume that the carbonyl derivative undergoes the *Re* face ylide addition (**TS8-*exo***), following the lowest energetic pathway, to give the major (*R*,*R*)-stilbene oxide. For this explanation, it is supposed that the downward methyl group of **8** shields the back face of these intermediates (Scheme 4). As far as the other dimethylthiolanes **2** and **5** are concerned, bearing a reverse absolute configuration at the α-position of the sulfur atom, they led to the opposite stereochemistry.

We desired to get insight in the relative position of the methyl groups at C2 and C5 of the thiolanium ring, with respect to the remote acetal bridge. We examined the optimized geometries of the most populated *exo* and *endo* ylides **8**, **9**,[21] and **10** (Table 4 and Scheme 5) by means of an ab initio computational study[12] at the HF/6-31G* level (see the Supporting Information for more details).[22]

The *exo* ylide species, having the phenyl pointing away from the bulky thiolane ring (the RR groups in Scheme 5), are slightly preferred conformations and the *exo* ylide **8** is the most stable. To have an indicator of the methyl position at C2, we took into account the dihedral angle θ (Table 4) between the downward methyl group at C2 and the methylene carbon of the ylides **8**−**10** as depicted in Scheme 5. The ylide **8**, having a pseudoaxial methyl group, features positive dihedral angles (Table 4, entry 1). As a consequence, the CH_3 is pulled backward from the methylene ylide carbon, lying underneath the five-membered ring. This conformation would therefore increase the 1,3 nonbonding interactions between the phenyl ring and the methyl group in the *endo*-ylide structure **8** and drive the equilibrium toward the *exo*-ylide **8**.[12b]

The ylides **9** and **10** are characterized by the two 2,5-methyl groups located in a pseudoequatorial position. The dihedral angles are positive (Table 4, entries 2 and 3). Since the ylides **9** and **10** feature reverse absolute configurations at C2 and C5 of the thiolane ring, the obtained conformation is different as can be seen in Scheme 5. Indeed, the downward CH_3 is pushed forward to the methylene ylide carbon. This conformation would minimize the 1,3 nonbonding interactions of the *endo*-ylides **9** and **10** and decrease the *endo*/*exo* equilibrium constant. Having this in mind, we assume that the pseudoaxial methyl groups could account for the selectivity of sulfide **4**, giving the corresponding ylide **8**. They could destabilize the **TS8-*endo*** transition state by 1,3 nonbonding interactions between the phenyl moiety and the downward CH_3 group (Scheme 4). It is also supposed that the pseudoaxial methyl group of **8** shields one of the ylide faces better than the pseudoequatorial methyl groups in analogues **9** and **10**. The difference in selectivity between **5** and **2** was not expected, according to the closely related structure of the corresponding ylide intermediates **9** and **10**. The derivative **2** is more flexible than **5** and likely features a different conformation in the transition state.

In summary, this work has provided insight into the importance of the conformation of C_2 symmetrical 2,5-dimethylthiolanes for the asymmetric synthesis of epoxides from chiral sulfonium ylide reagents. We have designed a locked chiral sulfide **4** with C2 and C5 methyl groups located in a pseudoaxial position. This original sulfur derivative promoted the synthesis of *trans*-aryl-epoxides with excellent enantiomeric ratios ranging from 95:05 to 98:02 via the catalytic transfer of benzylidene to a range of aromatic aldehydes. Moreover, under optimized conditions, making use of a phase transfer catalyst, n-Bu_4NHSO_4, the reaction was carried out with only 10−20% of chiral thiolane in 1 or 2 days in transition metal-free conditions. The novel chiral sulfur **4** is therefore one of the most selective and catalytically active promoter developed so far for the asymmetric synthesis of *trans*-stilbene oxide.[1] Although we do not reach the scope[23] of the recently developed metal-catalyzed carbenoid transfer toward chiral sulfonium ylide formation,[6a] our organocatalytic process constitutes an efficient one-pot procedure, which is easily performed in open reaction vessel with readily available and usually cheap materials.

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Supporting Information Available: Experimental procedures and characterization datas. Reproduction of ^{1}H NMR spectra for the sulfides **4** and **5**, the sulfonium salt derived from **4**, and the epoxides. Computational data for ylides **8**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For computational convenience, we replaced the *gem*-dimethyl group present on the acetal bridge of the sulfonium ylides **8** and **9** by a methylene group, given the lack of influence expected on the conformations.

(22) For discussion of such a computational method for sulfonium ylides, see: Lindvall, M. K.; Koskinen, A. M. P. *J. Org. Chem.* **1999**, *64*, 4596−4606.

(23) Under our conditions no epoxide was obtained from 3-pyridyl carboxaldehyde. 2-Thienyl carboxaldehyde underwent epoxidation in 20% yield after 3 days of reaction.