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CATALYTIC STEREOCONTROL OF A RADICAL CYCLIZATION

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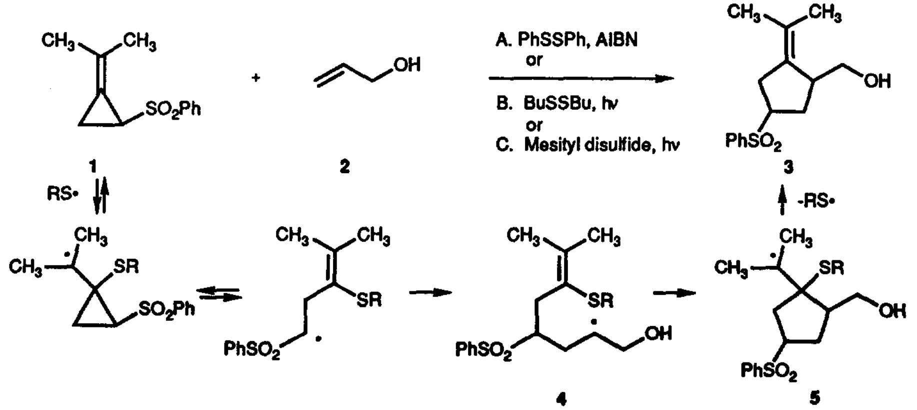
Summary: The stereochemistry of the free-radical chain mediated methylenecyclopentane annulation of olefins with 1 can be influenced significantly by the choice of catalyst radical. This suggests a new approach to the general problem of stereocontrol in radical reactions.

Radical-based synthetic methods often have some significant advantages over polar reactions in terms of range of tolerated functional groups and mildness of reaction conditions.[1] However, there are general problems with the stereocontrol of radical reactions, and this significantly limits their utility. Giese has stated: "Only when this problem [of stereoselectivity in radical reactions] is solved will it become possible to use free radicals widely in organic synthesis."[1b] The problem is compounded by the lack of counter-ion and solvent effects[2] which can control the stereochemistry of polar reactions. While considerable progress has been made in the design of stereoselectivity into radical reactions, the synthetic chemist has few "handles" on radical stereoselectivity, and can be faced with the task of varying his complex molecule to attempt stereocontrol, or restricted to loaded systems which can cyclize with only one stereochemistry.

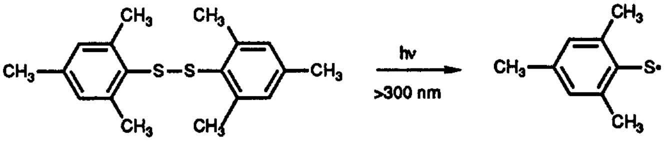
We have recently reported the thiyl-radical catalyzed [3+2] methylenecyclopentane annulations of olefins with methylenecyclopropanes.[3] This annulation is regiospecific, works under mild conditions without any need for protecting groups, can annulate equimolar amounts of the reacting olefin, and in the case of **1** can annulate unactivated olefins (e.g. **1** + **2** → **3**). A critical feature of the mechanism[4] (Scheme I) is that the catalyst is covalently bound to a reacting center during the cyclization of **4** to **5**, and it is at this step that the stereochemistry of the final product is determined. This suggested that the stereochemistry (cis vs. trans in **3**) could be influenced by changing the catalyst! This is a new concept in the stereocontrol of radical reactions, and we are pleased to report its validity.

Scheme I



We first noted a change in stereoselectivity in a control reaction in the absence of a source of thiyl radicals. The usual procedure for these reactions is to irradiate (>300 nm) n-butyl disulfide (10-25 mol %) to generate n-butylthiyl radicals[5] in a concentrated or neat mixture of **1**, olefin and 10 mol % pyridine. We were intrigued to find that the reaction of **1** with isobutyl vinyl ether still proceeded in the absence of n-butyl disulfide, albeit at a much slower rate. Further, the diastereomeric mixture of products in **6** varied reproducibly from 67% *cis* to 56% *cis* to 44% *cis* depending upon whether there was one equivalent, 10 mol %, or no n-butyl disulfide present, respectively (Table, entries 1-3). The identity of the catalyst radical in the absence of n-butyl disulfide is unknown, but a good possibility is phenylsulfonyl radical.[6] The most economical explanation for the change in stereochemistry is that, depending on the the amount of n-butyl disulfide present, the active catalyst may be n-butylthiyl radical, phenylsulfonyl radical, or a mixture of the two.

To more fully evaluate the potential for stereocontrol, we needed sterically diverse catalyst radicals. We had previously studied this annulation using both phenylthiyl radical (generated from phenyl disulfide/AIBN) and n-butylthiyl radicals as catalysts. With these two sterically similar catalysts, there was little difference in the stereochemistry of the products. Accordingly, we sought to catalyze the reaction with the sterically much more demanding *tert*-butylthiyl and mesitylthiyl (**7**) radicals. Irradiation of a reaction mixture containing *tert*-butyl disulfide succeeded in catalyzing the annulation of isobutyl vinyl ether with **1**, but failed in other reactions. Attempted reactions using mesityl disulfide/AIBN were not successful, but reactions employing irradiation of the mesityl disulfide worked very well. In fact, they were faster and generally cleaner than the butyl disulfide catalyzed reaction. In contrast, reactions employing irradiation of phenyl disulfide gave very low yields and complex mixtures.[7] The irradiation of the mesityl disulfide should find general utility in reactions employing thiyl radicals as catalysts. For example, Oshima had reported the reaction of **8** with 50 eq. of vinyl butyl ether affords a 17% yield of annulated products when catalyzed by thiophenol,[4b] but we obtained a 69% yield of a mixture of four isomers of **9** in the mesityl disulfide catalyzed reaction of **8** with 3 eq. of vinyl isobutyl ether.



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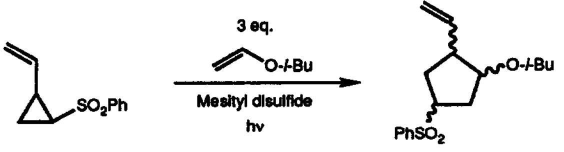
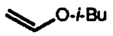
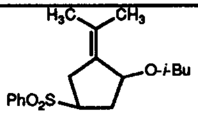
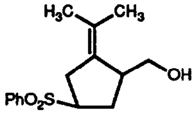
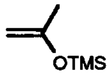
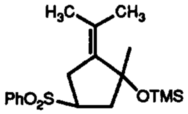
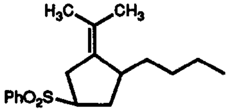


8 69% **9**

We were pleased to find that annulations of olefins with **1** employing mesityl disulfide afforded very different product ratios from those observed using butyl disulfide. Our results are summarized in the Table. The greatest increase in stereoselectivity came in the formation of **10** from isopropenoxytrimethylsilane, in which the product ratio increased from 61:39 to 92:8. Unfortunately, we have been unable to unambiguously

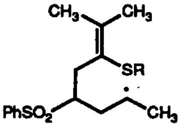
Table. Stereochemistry of Annulations

Olefin	Product	Disulfide	% Yield	cis:trans[a]	Entry
	 **6**	1 eq. *n*-butyl		67:33	1
		10 % *n*-butyl	81	56:44	2
		none		44:56	3
		tert-butyl	63	35:65	4
		mesityl	66	31:69	5
	 **3**	*n*-butyl	57	83:17	6
		mesityl	55	56:44	7
	 **10**	*n*-butyl	57	(61:39)[b]	8
		mesityl	51	(92:8)[b]	9
	 **11**	*n*-butyl	42	77:23	10
		mesityl	45	53:47	11

[a]The stereochemistry was assigned on the basis of NOE and equilibration studies, in reference 3.
[b]Stereochemistry not assigned.

assign the stereochemistry of the isomers in **10**. With the other olefins, there is a consistent increase in the amount of trans product formed.

To gain insight into our results, we carried out molecular mechanics calculations for the model cyclization of **12** (R = CH_2CH_3) using Houk's MM2 parameters for radical cyclization transition states.[8,9] The lowest energy transition state leading to each of the four possible cyclized diastereomers are depicted by **13-16**. Steric interactions between the alkylthio and methyl groups strongly destabilize **15** and **16**. The product stereochemistry is then determined by competition between the chair **13** which forms the cis product and the boat **14** which forms the trans product. It seems reasonable to expect that the boat **14** becomes more important as the size of R increases, which would explain the observed increase in trans product on increasing the size of R.



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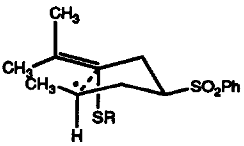

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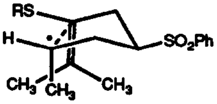

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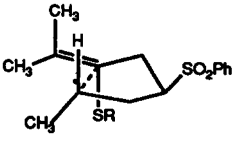

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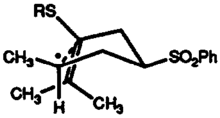

16

	13	14	15	16
Relative MM2 energy (kcal):	0.0	0.3	2.7	3.5

These results further expand the utility of our radical mediated annulation of unactivated olefins with methylenecyclopropanes. While the stereochemical changes observed here might not be considered large in polar reactions, they are unmatched in free-radical chain reactions. There is also clearly the potential for greater stereocontrol in other systems or using larger disulfides, and the potential for catalytic enantioselectivity. Finally, these results demonstrate a new concept in the stereocontrol of radical reactions which we think will be easily applicable to intermolecular radical reactions, and which we are vigorously pursuing.

Acknowledgment. Acknowledgment is made to The Robert A. Welch Foundation and the Donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

References and Notes

(1) For reviews of stereoselectivity in radical reactions, see: (a) Beckwith, A. L. J. *Tetrahedron* **1981,** *37,* 3073. (b) Giese, B. *Angew. Chem. Internat Ed Engl.* **1989,** *28,* 969.

(2) For exceptions when polar groups are present, see: Wujek, D. G.; Porter, N. A. *Tetrahedron,* **1985,** *41,* 3973. Giese, B.; Heuck, K.; Lenhardt, H. Lüning, U. *Chem. Ber.* **1984,** *117,* 2132.

(3) Singleton, D. A.; Church, K. M. *J. Org. Chem.* in press.

(4) For mechanistically similar reactions, see: (a) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988,** *110,* 3300. Feldman, K. S.; Ruckle, R. E., Jr. Romanelli, A. L. *Tetrahedron Lett.* **1989,** *30,* 5845. Feldman, K. S.; Fisher, T. E. *Tetrahedron* **1989,** *45,* 2969. Feldman, K. S.; Simpson, R. E. *Tetrahedron Lett.* **1989,** *30,* 6985. (b) Miura, K. Fugami, K. Oshima, K. Utimoto, K. *Tetrahedron Lett.* **1988,** *29,* 5135.

(5) Rao, P. M.; Knight, A. R. *Can. J. Chem.* **1968,** *46,* 2462.

(6) These reactions can be catalyzed by irradiation of diphenyl disulphone, but acid-catalyzed reactions appear to quickly ensue.

(7) Irradiation of phenyl disulfide results in a photo-Fries type rearrangement, and the resulting 2-phenylthio thiophenol can rapidly donate hydrogen to any radical in solution. This rearrangement does not occur in mesityl disulfide. See: Schaafsma, Y.; Bickel, A. F.; Kooyman, E. C. *Tetrahedron* **1960,** *10,* 76.

(8) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987,** *52,* 959.

(9) A variety of MM2 parameters produced qualitatively the same results, that is, **13** and **14** close in energy, and much more stable than **15** and **16**. For the results listed, the sulfur attached to the alkene atom being attacked (C_a) was equivalenced to an sp^3 carbon for the torsional and bending parameters Houk developed.[8] The torsional parameters for $C\bullet$-C_a-S-C were set at $V_1=V_3=0$, $V_2=-2.0$, qualitatively based on MNDO calculations for the addition of methyl radical to ethylene thiol. The remaining parameters were set, following Houk's procedure, by considering C_a as a normal sp^3 carbon.

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