This unexpected observation perhaps could be attributed to the arising of a severe $A^{(1,3)}$ allylic strain[11] if **13** is forced to adopt the conformation with the C–H bond of the methine hydrogen parallel to the C–C π bonds. Such a conformation would be required in the transition states of the initiation and the propagation steps leading to the corresponding benzylic radical in order for them to benefit from aromaticity. It is likely that the benzylic radical center in the transition states would be pushed away from the parallel position with the C–C π bonds of the benzene ring, resulting in the loss of the resonance energy and the increase of the energy barrier. Consequently, **13** is much more stable than **12** toward air. On the other hand, **12** is free from severe allylic strain, and therefore is prone to autoxidation.

In summary, the reaction sequence outlined in Schemes I and II could be easily adopted for the synthesis of a variety of *o*-isotoluenes and diene–allenes by using different combinations of readily avalable γ-(trimethylsilyl)allylboranes and conjugated allenic aldehydes. With the development of such a facile route to *o*-isotoluenes, the chemical properties of these compounds can now be investigated and the large amount of energy (ca. 24 kcal/mol)[4b] to be gained from aromatization is ready to be exploited. The conjugated diene–allenes are synthetically useful for the preparation of polyenes through facile sigmatropic hydrogen shifts[12] and can also find applications in the Diels–Alder reaction utilizing the allene moiety as a part of the diene component.[6a,13]

Acknowledgment. The financial support of the National Science Foundation for the purchase of a JEOL GX-270 NMR spectrometer (RII-8011453) and an HP 5970B GC/MSD system (CHE-8913626) is gratefully acknowledged.

Supplementary Material Available: Experimental procedures, IR, MS, ^1H NMR, and ^{13}C NMR spectral data and actual ^1H and ^{13}C NMR spectra of **8**, **9**, **12**, **13**, **14**, **15**, **18**, **20** (23 pages). Ordering information is given on any current masthead page.

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(11) (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

(12) Sueiras, J.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6255–6259.

(13) (a) Snider, B. B.; Burbaum, B. W. *J. Org. Chem.* **1983**, *48*, 4370–4374. (b) Reich, H. J.; Eisenhart, E. K. *J. Org. Chem.* **1984**, *49*, 5282–5283. (c) Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487–2493. (d) Wang, K. K.; Andemichael, Y. W.; Dhumrongvaraporn, S. *Tetrahedron Lett.* **1989**, *30*, 1311–1314. (e) Curtin, M. L.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 5278–5287.

Diastereoselectivity in the Hydroxyl-Directed Cyclopropanation of Vinylorganometallic Compounds

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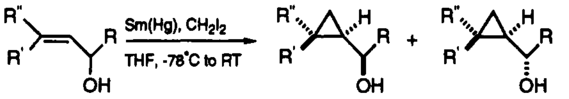
Received October 29, 1991

Summary: Olefins bearing silicon and/or tin substituents undergo highly diastereoselective cyclopropanation in the presence of Sm/CH_2I_2. The stereochemistry of the tin moiety has a dramatic effect on the rate of a subsequent transmetalation with MeLi.

Hydroxyl-directed reactions have found widespread use in organic synthesis. The directed epoxidation, osmylation, and hydrogenation reactions are a few of the now standard methods for the construction of multiple adjacent stereocenters.[2-4] Directed cyclopropanation reactions are also well-known and are of current interest.[5] Molander has recently reported highly diastereoselective cyclopropanation of allylic alcohols using Sm/CH_2I_2, eq 1.[6] The results of these studies may be summarized as follows: *Z* olefins undergo diastereoselective cyclopropanation with de's >100:1; *E* olefins also undergo cyclopropanation with selectivities which increase as the steric sizes of R and R″ increase. When R is small, the facial selectivity is reversed and modest selectivities are obtained (approximately 1:4–6).



(1)

In light of the demonstrated utility of silylated[7] and stannylated[8] cyclopropanes, and our interest in the preparation of 1,1-dimetalated olefines bearing tin and/or silicon,[9] we undertook a study to evaluate the reactivity

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(1) A. P. Sloan Foundation Fellow, 1991–93; NSERC (Canada) University Research Fellow 1987–1992; Bio-Mega Young Investigator 1990–1993.

(2) (a) Finn, M. G.; Sharpless, K. B. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985. (b) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(3) Osmylation of allylic alcohols: (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943, 3947. (b) Vedejs, E.; Dent, W. H., III. *J. Am. Chem. Soc.* **1989**, *111*, 6861. (c) Panek, J. S.; Cirillo, P. F. *Ibid.* **1990**, *112*, 4873. (d) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 1698 and references cited therein.

(4) For a review on the directed hydrogenation, see: Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190. (a) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348. (b) Brown, J. M.; Hall, S. A. *J. Organomet. Chem.* **1985**, *285*, 333. (c) Crabtree, R. H.; Davis, M. W. *Organometallics* **1983**, *2*, 681. (d) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655. (e) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. (f) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866. (g) Evans, D. A.; Morrissey, M. M. *Tetrahedron Lett.* **1984**, *25*, 4637. (h) Evans, D. A.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476. (i) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. (j) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596, 4129. (k) Kitamura, M.; Nagai, K.; Hsiao, Y.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 549.

(5) For leading references, see ref 4 and: (a) Mohamadi, F.; Still, W. C. *Tetrahedron Lett.* **1986**, *27*, 893. (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256.

(6) (a) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, *52*, 3942. (b) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525. For other stereoselective cyclopropanations using samarium see: (c) Clive, D. L. J.; Daigneault, S. *J. Org. Chem.* **1991**, *56*, 3801. (d) Kabat, M.; Kiegiel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1991**, *32*, 2343.

(7) Paquette, L. A. *Chem. Rev.* **1986**, *86*, 733 and references cited therein.

(8) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2415.

and diastereoselectivity of metalated substrates under the Molander cyclopropanation reaction conditions.[10] We report that these metalated olefins react with high diastereoselectivity providing highly functionalized cyclopropanes. Furthermore, we show that the stannylated cyclopropanes can be transmetalated and the resulting lithium anion reacted with electrophiles, thereby providing access to diastereomers unavailable by the direct cyclopropanation.

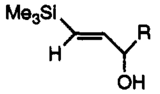
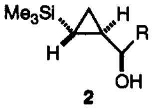
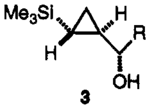
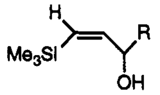
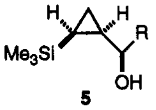
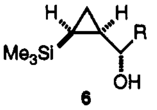
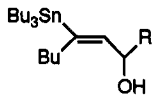
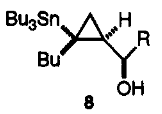
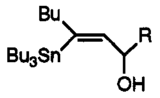
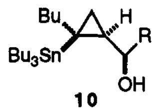
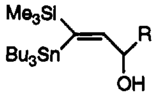
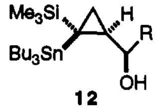
The *E*-stannylated and 1,1-dimetalated substrates **7a,b** and **11a–c** were prepared using our modification of the Sato reaction,[9,11] which involves treatment of a propargylic alcohol with Cp_2TiCl_2/*i*-BuMgCl followed by trapping the resulting vinylmagnesium species with tributyltin chloride. Vinylsilanes **1a–c** and **4a,b** and (*Z*)-stannylallylic alcohol **9** were prepared by literature methods.[12]

The optimum conditions for cyclopropanation were established using (*E*)-vinylsilane **1a**. Under the conditions described by Molander (4 equiv of Sm, 4 equiv of CH_2I_2), low yields of the desired cyclopropane **2a** were obtained. By increasing to 10 equiv of the samarium reagent and running the reaction at higher concentration (0.13 M), the yield improved to 81% and the diastereoselectivity was excellent (46:1, Table I, entry 1). Oxidation of the cyclopropyl alcohol to a ketone (PCC, NaOAc) followed by nonselective reduction ($LiAlH_4$) generated authentic mixtures of diastereomers. Purification of the two alcohols (which were usually well-separated by TLC) and comparison of their NMR spectra and GC retention times allowed us to determine the level of diastereoselection in the directed cyclopropanation. We found that decreasing the steric bulk of the R group from cyclohexyl to *n*-propyl to methyl affected the sense and level of diastereoselection. The diastereoselectivity *decreases and reversed in this series.*

Substrates with a *Z* substituent react to give the cyclopropanes in much higher selectivity than those with only an *E* substituent, and the selectivity is not dependent on the size of the R group. Thus, vinylsilanes **4a,b** gave **5a,b** with selectivities of >100:1 (entries 4 and 5). Molander has proposed transition-state structures based on the Houk model to provide an explanation for the observed diastereoselectivity for the *Z* isomer.[6,13] Minimization of steric interactions between the R group and the cis substituent, coupled with complexation between the hydroxyl group and the incoming carbenoid, differentiates the two possible transition structures.

Trisubstituted olefins bearing a tin or alkyl group cis to the hydroxyalkyl chain react with the cyclopropanating agent to yield a single diastereomer in good yield (entries 6–11). Comparison of the selectivity in entries 3 and 11 demonstrates that replacement of a hydrogen by a tin moiety completely reverses the sense of diastereoselection, indicating the importance of the cis substituent in controlling the favored reactive conformer.[14]

Table I. Directed Cyclopropanation of γ-Hydroxyvinylsilanes and -stannanes[a]

entry	substrate		product[1] diastereoselectivity[2]			yield[3,4]
			 **2**		 **3**	
1	**1a**	R = Cyclohexyl	46	:	1	81%[*,5]
2	**b**	Pr	1	:	1.3	84%[6]
3	**c**	Me	1	:	10	76%
			 **5**		 **6**	
4	**4a**	R = Pr	>100	:	1	67%
5	**b**	Me	>100	:	1	67%[7]
				 **8**		
6	**7a**	R = Cyclohexyl				75% (92%)[*,8]
7	**b**	Me				80%[8]
				 **10**		
8	**9**	R = Cyclohexyl				27%[*,8,9,10]
				 **12**		
9	**11a**	R = Cyclohexyl				80%[8]
10	**b**	Pr				67% (82%)[8]
11	**c**	Me				65%[8]

[a] Key: (1) Typical reaction conditions involve treatment of the allylic alcohol with 8–10 eqiv of $Sm(HgCl_2)$ in THF, followed by dropwise addition of CH_2I_2 at −78 °C. The reaction mixture was allowed to warm to rt over 2 h followed by another 2–20 h of stirring. See supplementary material. (2) Diastereoselectivities determined by CGC, using a Carbowax HP-20M column, unless noted otherwise. (3) Isolated yield of pure product following flash chromatography. (4) Yields in parenthesis are based on unreacted starting material. (5) Yields marked with an asterisk (*) were obtained from reactions performed with samarium from Rhone Poulenc (Phoenix, AZ). In all other cases, samarium from Aldrich was used. (6) The assignment of the major and minor isomers may be reversed. (7) Diastereoselectivity determined by CGC, using a Silicone HP-5 column. (8) Only one diastereoisomer was observed. (9) 58% yield of the destannylated material was also isolated (as a single diastereomer). (10) See ref 19.

Transmetalation of tin-containing cyclopropanes was investigated.[8,14,15] Following conversion of **12a** to its

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(9) (a) Lautens, M.; Huboux, A. H. *Tetrahedron Lett.* **1990**, *31*, 3105. (b) Lautens, M.; Huboux, A. H.; Chin, B.; Downer, J. *Tetrahedron Lett.* **1990**, *31*, 5829.

(10) A decrease in reactivity has been noted in the cyclopropanation of monosilyl-substituted olefins, see: Seyferth, D.; Burlitch, J. M.; Minasz, R. J.; Mui, J. Y.-P.; Simmons, H. D., Jr.; Treiber, A. J. H.; Dowd, S. R. *J. Am. Chem. Soc.* **1965**, *87*, 4259 and ref 7.

(11) The hydromagnesiation of a propargylic alcohol catalyzed by titanium was first reported by Sato, see: (a) Sato, F. *J. Organomet. Chem.* **1985**, *285*, 53. (b) Sato, F.; Watanabe, H.; Tanaka, Y.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1126. (c) Sato, F.; Kobayashi, Y. *Org. Synth.* **1990**, *69*, 106.

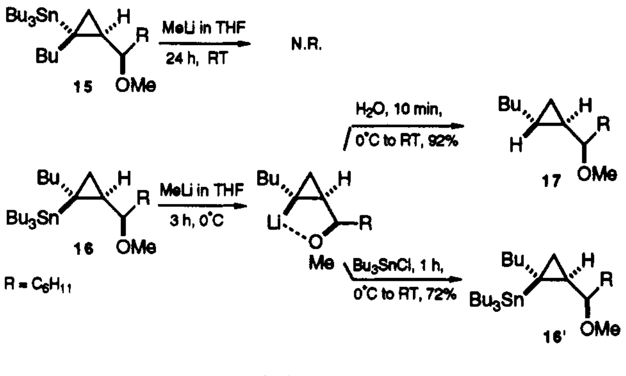
(12) For the preparation of (*E*)-vinylsilanes, see ref 11b. (*Z*)-Vinylsilanes: Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, 553. (*Z*)-Stannylalkyl-substituted olefin: Piers, E.; Tillyer, R. D. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2124.

(13) (a) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162. (b) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257. (c) Mareda, J.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1983**, *105*, 6997.

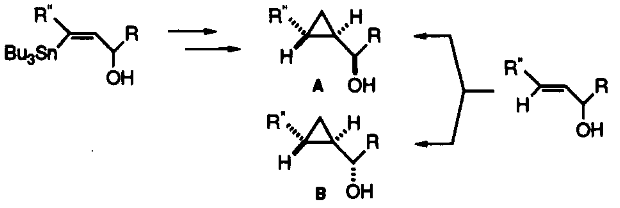
(14) Oxidation of **8**, **10**, or **12** (i.e., those substrates with a tin substituent) with PCC was complicated by side reactions. For example, oxidation of **8a** gave the desired cyclopropyl ketone and cyclohexyl 2-methylenylhexyl ketone. Attempted oxidation of **12a** gave a complicated mixture of products. The presence of a substituent appears to be responsible for these side reactions, see: Piers, E.; Jean, M.; Marrs, P. S. *Tetrahedron Lett.* **1987**, *28*, 5075.

(15) For related transmetalations of α-stannylsilanes, see: Barrett, A. G. M.; Hill, J. M. *Tetrahedron Lett.* **1991**, *32*, 3285. Barrett, A. G. M.; Hill, J. M.; Wallace, E. M.; Flygare, J. A. *Synlett* **1991**, 764.

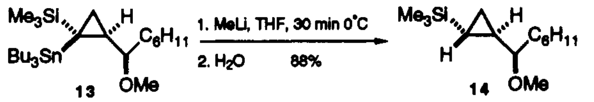
Scheme I



Scheme II



methyl ether 13 (MeI, KH, THF), rapid lithium exchange occurred (MeLi, THF, 0 °C) providing 14 in 88% yield, eq 2.[16] The solvent plays a critical role in the transmetalation since reaction in hexanes or ether was ineffective. The relative stereochemistries of the tin- and alkoxy-bearing side chains were also found to have a significant effect on the rate of transmetalation, indicating that chelation plays a role in the exchange process.[17] Reaction of the *E* isomer 15 with methyllithium gave <10% conversion even after 24 h at rt. However, treatment of the *Z* isomer 16 with methyllithium in THF at 0 °C was complete in 3 h.[18] The lithium anion was trapped with electrophiles (H_2O and Bu_3SnCl) providing 17 and 16′ in 92 and 72% yields, respectively, as shown in Scheme I. Comparison of the ^{13}C and ^{119}Sn NMR of 16′ with both 15 and 16 clearly showed that 16 and 16′ were identical, and thus the transmetalation and restannylation occurred with overall retention of configuration. This observation allowed us to establish that the major diastereomer resulting from of cyclopropanation of 1c was reversed compared to 1a. Treatment of 12c with excess methyllithium, followed by trapping the dianion with water, yielded 2c rather than 3c as demonstrated by comparison of the ^{1}H NMR spectra and CGC retention times.


(2)

This transmetalation–protonation sequence is important since, as noted in the introduction, the diastereoselectivity of the directed cyclopropanation is moderate and reversed for simple *E* olefins when R or R″ is small (i.e., **B** is formed preferentially). Access to **A** the diastereomer which is not available from a direct cyclopropanation, is feasible by removal of the tin moiety following cyclopropanation for R″ = alkyl or TMS (Scheme II). Thus, the tin moiety acts as a removable group which controls the diastereoselectivity. Further research using these dimetalated cyclopropanes in synthesis is in progress.

Acknowledgment. We thank the A. P. Sloan Foundation, the Natural Science and Engineering Research Council (NSERC) of Canada, Bio-Mega, the Merck Frosst Centre for Therapeutic Research, and the University of Toronto for financial support. P.H.M.D. thanks the University of Toronto for a Simcoe Scholarship.

Supplementary Material Available: General experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for the prepared compounds (15 pages). This materials is contained in many 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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(16) Trapping of the anion with methyl iodide successfully led to the methyl-substituted cyclopropane.

(17) Carpenter has observed a similar correlation of hydroxyl stereochemistry with the rate of tin–lithium exchange in a conformationally fixed ring system. A further rate increase for transmetalation 13 could be due to the α-stabilizing effect of the silicon group. (a) Newman-Evans, R. H.; Carpenter, B. K. *Tetrahedron Lett.* **1985**, *26*, 1141. For an example of a directed halogen–metal exchange, see: (b) Hiyama, T.; Kanakura, A.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1978**, 3047.

(18) Treatment of 15 with 10 equivs of *n*-BuLi in THF for 10 h did lead to complete transmetalation. A full discussion of the effect of organolithium reagent, solvent, and substrate geometry will be presented in the full paper.

(19) Decreasing the steric bulk from cyclohexyl to methyl led to a considerably higher yield in the cyclopropanation of these (*Z*)-stannyl alkenes, and no destannylated product was observed. A discussion will be presented in the full paper.