Regioselective Cyclopropanation of α-Allenic Alcohols. An Efficient Route to Alkylidenecyclopropanes

Mark Lautens*[1a] and Patrick H. M. Delanghe[1b]

Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 1A1

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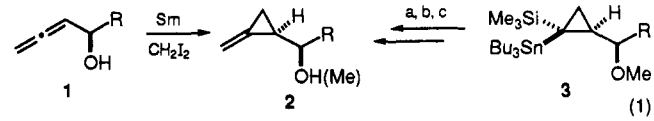
Summary: Highly substituted alkylidenecyclopropanes are now easily accessible via a regioselective cyclopropanation of α-allenic alcohols using samarium/CH_2I_2. Dienols provide vinylcyclopropylcarbinols upon methylenation.

Alkylidenecyclopropanes have been the subject of intensive study over the last 25 years from the mechanistic,[2] biological,[3] and synthetic perspectives.[4] One particularly important reaction of methylenecyclopropanes, the metal-catalyzed insertion into the cyclopropane using Ni or Pd, followed by treatment with alkenes or alkynes, provides an efficient route for the synthesis of 5-membered rings.[4] As part of a program directed toward the study of metal-catalyzed cycloadditions of highly functionalized methylenecyclopropanes, we required an efficient synthesis of this class of compounds. Although various routes toward simple, symmetrical methylenecyclopropanes have been described, few of the methods are applicable to the convenient preparation of the more substituted methylenecyclopropylcarbinols such as **2**.[5] We now describe two routes to methylenecyclopropanes which are complimentary and make these compounds readily available in diastereomerically and enantiomerically enriched form for the first time.

Our first route to the alkylidenecyclopropane carbinols was realized starting from the stannylsilylcyclopropane **3** which can be obtained in good yield and diastereoselectivity via a samarium-promoted cyclopropanation of a heterobimetallic allylic alcohol.[6,7] The silyl lithiocyclopropane, obtained from a tin-lithium exchange, was trapped by paraformaldehyde, and the resulting silyl cyclopropyl carbinol was converted into the methylenecyclopropanes via a Peterson elimination (i.e., **3** to **2**).[8]

Scheme I[a]



(1)

[a] Key: (a) Sn-Li exchange; (b) aldehyde addition; (c) Peterson elimination.

Although this procedure was satisfactory, we were intrigued by the possibility of a more direct approach to **2** using a hydroxyl-directed cyclopropanation of an α-allenic alcohol (i.e., **1** to **2**).[9] Cyclopropanation of α-allenic alcohols was first reported in 1967 by Bertrand and Maurin using the classical Simmons-Smith conditions.[10,11] Unfortunately, equimolar mixtures of methylenecyclopropane and spiropentanes were obtained. Furthermore, little or no diastereoselectivity was observed. We reinvestigated this procedure along with several more recent modifications of the Simmons-Smith process with disappointing results.[12] More recently, Molander showed that a nearby hydroxyl group is essential for the samarium-promoted cyclopropanation when geraniol underwent selective reaction on the olefin proximal to the hydroxyl functionality.[6] In our hands, cyclopropanation of an unhindered homoallylic substrate, 1-cyclohexyl-3-buten-1-ol, resulted in only 27% yield of the cyclopropane, along with recovered starting material. Moreover, no reaction was observed when cyclopropanation of an allylic methyl ether, e.g., (*E*)-1-cyclohexyl-3-(trimethylsilyl)prop-2-enyl methyl ether was attempted, again indicating the importance of the hydroxyl moiety.

When we carried out the cyclopropanation of allenic alcohol **1b** (R = cyclohexyl) using samarium/di-

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(1) (a) Alfred P. Sloan Foundation Fellow 1991-1994, NSERC (Canada) University Research Fellow 1987-1997, Bio-Mega Young Investigator 1990-1993, Eli Lilly Grantee 1992-1994. (b) Simcoe Scholar 1991-1993, Ontario Graduate Scholar 1993-1994.

(2) (a) Dewar, M. J. S.; Wasson, J. S. *J. Am. Chem. Soc.* **1971**, *93*, 3081. (b) Lazzara, M. G.; Harrison, J. J.; Rule, M.; Hilinski, E. F.; Berson, J. A. *Ibid.* **1982**, *104*, 2233.

(3) Baldwin, J. E.; Widdison, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 2245 and references cited therein.

(4) (a) Noyori, R.; Odagi, T.; Takaya, H. *J. Am. Chem. Soc.* **1970**, *92*, 5780. (b) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (c) Ohta, T.; Takaya, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 1185. (d) Motherwell, W. B.; Shipman, M. *Tetrahedron Lett.* **1991**, *32*, 1103 and references cited therein. For an alternative approach, see: Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1.

(5) For a stereorandom synthesis of similar compounds, see: Thomas, E. W. *Tetrahedron Lett.* **1983**, *24*, 1467. For recent reports of substituted methylenecyclopropane synthesis, see ref 8 and: (a) Piers, E.; Gavai, A. V. *J. Org. Chem.* **1990**, *55*, 2380. (b) Hsiao, C.-N.; Hannick, S. M. *Tetrahedron Lett.* **1990**, *31*, 6609. (c) Kabat, M. M.; Wicha, J. *Tetrahedron Lett.* **1991**, *32*, 531. (d) Satoh, T.; Kawase, Y.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1129. (e) Lai, M.; Oh, E.; Shih, Y.; Liu, H. *J. Org. Chem.* **1992**, *57*, 2471. (f) Baldwin, J. E.; Adlington, R. M.; Bebbington, D.; Russell, A. T. *J. Chem. Soc., Chem. Commun.* **1992**, 1249. (g) Stolle, A.; Ollivier, J.; Piras, P. P.; Salaün, J.; de Meijere, A. *J. Am. Chem. Soc.* **1992**, *114*, 4051. (h) Prieto, J. A.; Pallares, T.; Larson, G. L. *Synlett* **1993**, 199.

(6) (a) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, *52*, 3942. (b) Molander, G. A.; Harring, L. S. *Ibid.* **1989**, *54*, 3525.

(7) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1992**, *57*, 798.

(8) Alkylidenecyclopropane synthesis via α-lithio-α-silyl cyclopropanes followed by a Peterson olefination: (a) Halazy, S.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1981**, *22*, 4737. (b) Hiyama, T.; Kanakura, A.; Morizawa, Y.; Nozaki, H. *Ibid.* **1982**, *23*, 1279.

(9) For a comprehensive review of substrate-directable reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

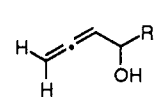
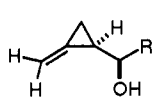
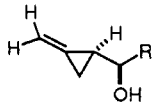
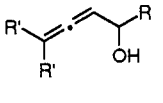
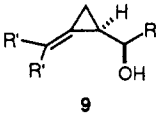
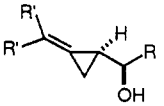
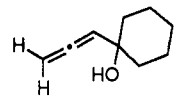
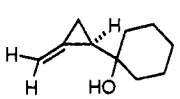
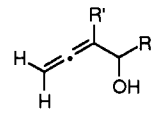
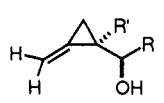
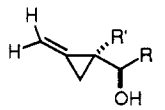
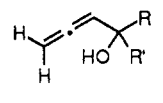
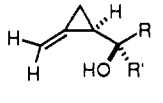
(10) For a recent review, see: Helquist, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 968 and references cited therein. For a recent discussion on the (iodomethyl)zinc reagent, see: Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6975. See also: (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256. (b) LeGoff, E. *J. Org. Chem.* **1965**, *29*, 2048. (c) Nishimura, J.; Kawabata, N.; Furakawa, J. *Tetrahedron* **1969**, *25*, 2647. (d) Rawson, R. J.; Harrison, I. T. *J. Org. Chem.* **1970**, *35*, 2057. (e) Denis, J. M.; Girard, C.; Conia, J. M. *Synthesis* **1972**, 549. (f) Maruoka, K.; Fukutani, Y.; Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 4412. For the first hydroxyl-directed cyclopropanation of allylic alcohols: (g) Winstein, S.; Sonnenberg, J.; de Vries, L. *J. Am. Chem. Soc.* **1959**, *81*, 6523. (h) Winstein, S.; Sonnenberg, J. *Ibid.* **1961**, *83*, 3235.

(11) (a) Bertrand, M.; Maurin, R. *Bull. Soc. Chim. Fr.* **1967**, 2779. (b) Maurin, R.; Bertrand, M. *Ibid.* **1970**, 2261. For an earlier, nonregioselective cyclopropanation of an allene using Zn/Cu, see: Ullman, E. F.; Fanshawe, W. J. *J. Am. Chem. Soc.* **1961**, *83*, 2379.

(12) For example, Zn/Cu and Et_2Zn gave 1:2.7 and 1:1.2 mixtures of mono- and dicyclopropanation products, respectively, when the reaction was run to completion.

0022-3263/93/1958-5037$04.00/0

Table I. Directed Cyclopropanation of α-Allenic Alcohols

entry	substrate	product diastereoselectivity[a]			yield[b]
		 **2**		 **7**	
1	**1a** R = t-butyl	50	:	1	57%
2	**b** c-hexyl	9.5	:	1	64%
3	**c** i-propyl	4.0	:	1	40%
4	**d** n-heptyl	1	:	2.1	73%
		 **9**		 **10**	
5	**8** R = c-hexyl, R' = n-propyl	1.7	:	1	43%
		 **12**			
6	**11**				30%
		 **14**		 **15**	
7	**13a** R = c-hexyl, R' = Me	7.9	:	1	66%[c,d]
8	**b** c-hexyl, R' = MeO	50	:	1	47%[d]
9	**c** n-heptyl, R' = MeO	13	:	1	59%[d]
		 **17**			
10	**16** R = i-propyl, R' = methyl				46%

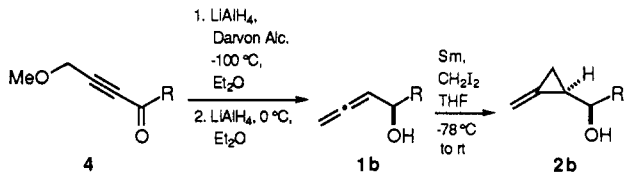
[a] Diastereomeric ratio's determined by CGC, using a Carbowax HP-20M column unless noted otherwise. [b] Isolated yield of pure product. [c] Stereochemistry assigned following comparison of ^{1}H NMR and GPC/TLC retention times and by analogy to **2b** and **14b**. [d] Diastereomeric ratio determined by ^{1}H NMR (400 MHz).

iodomethane, the reaction was found to be highly regioselective (>70:1) and diastereoselective. Encouraged by this remarkable increase in selectivity, we investigated the generality of this process.[13] As can be seen from Table I, a variety of allenes can be cyclopropanated in moderate to good yields, depending on the steric hindrance at the carbinol carbon. Importantly, the reaction is applicable for the synthesis of simple and more functionalized alkylidenecyclopropanes (entries 7–9).

The diastereoselectivity for unsubstituted and terminally substituted allenic alcohols depends on the size of the carbinol side chain (R group). The selectivity increased in the series isopropyl (4.0:1), cyclohexyl (9.5:1), *tert*-butyl (50:1), leading to synthetically useful levels of selectivity (entries 1–3). An *n*-alkyl group gave low and opposite selectivity, a trend which has been previously observed in samarium cyclopropanations.[6,7] Assignment of the relative stereochemistry of the major diastereomer was achieved by comparison with a sample prepared from the stannylsilylcyclopropane **3** whose stereochemistry was previously determined, eq 1 (Scheme I).[7] It is interesting to observe that when the hydrogens on the terminal position are substituted for two alkyl chains, the selectivity drops from 9.5 to 1.7:1 (compare entries 2 and 5).

For 1,1-disubstituted allenes **13a–c**, nonbonded steric interactions between R and R' (1,2 interaction) appear to be less important than electronic effects (compare entries 2 and 7 vs 8). Good (7.9:1) to excellent levels (50:1) of selectivity are obtained. The relative stereochemistry of **14b** was confirmed by X-ray crystallography.[14]

We have also developed a modified route to the starting α-allenic alcohols in enantiomerically enriched form via a one-pot, two-step protocol, eq 2. This sequence begins



4 → **1b** → **2b**

R = C_6H_{11} 67% 85% ee 64% 84% ee (2)

with an enantioselective reduction of the ynone with $LiAlH_4$/Darvon alcohol at −110 to −100 °C.[15] After the ynone is completely consumed, the reaction is warmed to 0 °C and a second equivalent of $LiAlH_4$ is added. Displacement of the propargylic methoxy group by a hydride occurs in the second step. It is interesting to note that no displacement occurs without additional $LiAlH_4$. α-Allenic alcohols are thus obtained in good yield with ee's between 85 and 93%.[16,17] The enantiomeric purity was maintained during the subsequent cyclopropanation of **1b** to **2b**.

In light of the utility of vinylcyclopropanes in organic chemistry,[18,19] we briefly examined the cyclopropanation of 2,4-hexadien-1-ol using the Sm/CH_2I_2 conditions.[20] The reaction was extremely selective toward the alkene proximal to the hydroxyl group, and the isolated yield of **6** was

(13) All racemic α-allenic alcohols were easily prepared in one or two steps, starting from an aldehyde and an organometallic allene or alkyne. (a) Cowie, J. S.; Landor, P. D.; Landor, S. R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 720. (b) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: Amsterdam, 1981, p 43. (c) Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225.

(14) Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. For the other products the stereochemistry was assigned following comparison of their ^{1}H NMR spectra (chemical shifts and NOE measurements) as well as GPC/TLC retention times.

(15) Either enantiomeric propargyl alcohol can be prepared in high ee via this reaction. (a) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870. (b) Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339. For a recent example, see: Marshall, J. A.; Salovich, J. M.; Shearer, B. G. *J. Org. Chem.* **1990**, *55*, 2398.

(16) Approximately 20% of an allylic alcohol, formed from a competing hydroalumination reaction, was also observed when the allenic alcohol was prepared via the two-step, one-pot sequence.

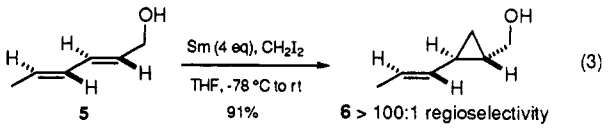
(17) For another strategy yielding highly enantiomerically enriched α-allenic alcohols, see: Corey, E. J.; Yu, C.-M.; Lee, D.-H. *J. Am. Chem. Soc.* **1990**, *112*, 878.

(18) (a) Reissig, H.-U. *The Chemistry of the Cyclopropyl Group*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1987; Part 1, p 416. (b) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247. (c) Salaün, J. R. Y. *Top. Curr. Chem.* **1988**, *144*, 1.

(19) For an extensive list of references to other methods of vinylcyclopropane synthesis and their reactions, see: (a) Schaumann, E.; Kirschning, A.; Narjes, F. *J. Org. Chem.* **1991**, *56*, 717. (b) Buchert, H.; Reissig, H.-U. *Chem. Ber.* **1992**, *125*, 2723.

(20) For previous reports of hydroxyl-directed monocyclopropanation of dienols under the Simmons–Smith conditions, see: (a) Corey, E. J.; Yamamoto, H.; Herron, D. K.; Achiwa, K. *J. Am. Chem. Soc.* **1970**, *92*, 6635. (b) Barbachyn, M. R.; Johnson, C. R.; Glick, M. D. *J. Org. Chem.* **1984**, *49*, 2746.

91%, eq 3.[21] We could not detect any doubly cyclopropanated product.



5 91% 6 > 100:1 regioselectivity (3)

In conclusion, we have reported the regio- and diastereoselective cyclopropanation of allenic alcohols and a dienol and shown that the samarium-promoted cyclopropanation reaction is remarkably sensitive to the orientation of the hydroxyl and olefinic moieties. We have also shown that a one-pot combination of the Mosher and Landor reductions leads to an efficient synthesis of the allenic alcohols in enantiomerically enriched form. Utilization of the products in cycloaddition reactions is underway.

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Supplementary Material Available: Experimental procedures, ^1H and ^{13}C NMR, IR, and mass spectral data for the methylenecyclopropanes, and data for the X-ray structure of **14b** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal and can be ordered from the ACS; see any current masthead page for ordering information.

(21) Cyclopropanation of (*E,E*)-2,4-hexadien-1-ol promoted by a Zn/Cu couple was examined using the conditions described by Harrison and Rawson.[10d] Using 6 equiv of Zn/Cu and 6 equiv of CH_2I_2 for 24 h gave exclusively the doubly cyclopropanated alcohol in 21% isolated yield. Use of 1 equiv of CH_2I_2 and 3 equiv of Zn/Cu in refluxing ether for 20 h gave no reaction. Addition of a further 1.3 equiv of CH_2I_2 to the same reaction gave predominantly **6** with some unreacted starting material and doubly cyclopropanated product which could not be separated.