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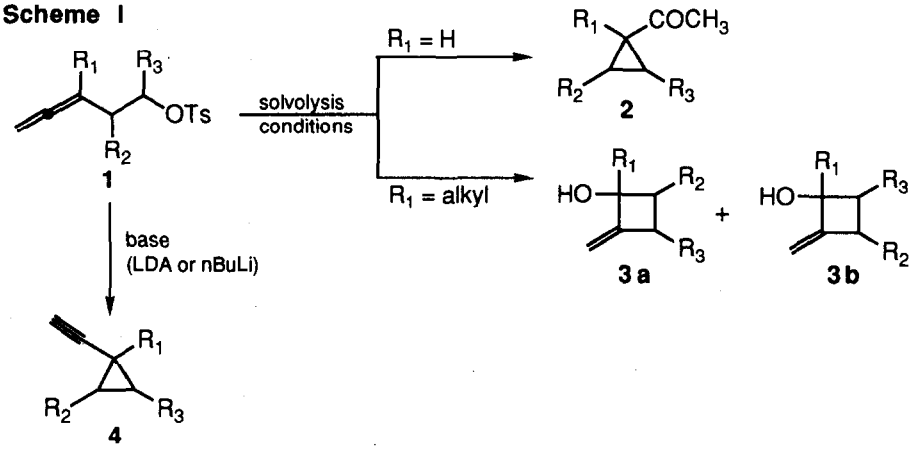
AN IMPROVED SYNTHESIS OF CYCLOPROPANES FROM HOMOALLENIC ALCOHOLS

Sungsoo Pyo,[1b] Joseph F. Skowron III,[1c] and Jin K. Cha*,[1a]
Department of Chemistry, Vanderbilt University, Nashville, TN 37235, U.S.A.

Abstract: Treatment of the readily available β-allene tosylates with LDA or nBuLi provides an expeditious, although stereorandom, synthesis of functionalized cyclopropanes which can be easily prepared in high enantiomeric purity.

Homoallenic groups are well-known to participate in solvolysis reactions in a manner analogous to homoallylic groups. For example, β-allenic tosylates or halides (**1**) are readily cyclized under solvolytic conditions to afford cyclopropylketones (**2**) or methylenecyclobutanols (**3**) as the major product, mainly depending upon the R_1 substituent of the starting allenes (Scheme I).[2] By taking advantage of the relative acidity of the allenyl proton, it occurred to us that treatment of these β-allene tosylates with a base should furnish alkynylcyclopropanes (**4**) with clean inversion of configuration at the sp^3 carbon center.[3] This ring formation would lend itself to the synthesis of enantiomerically pure cyclopropanes of defined absolute stereochemistry from the readily available β-allenic alcohols.[4,5] Herein we report the successful implementation of such approach to an expeditious, although stereorandom, synthesis of functionalized cyclopropanes which can be easily prepared in high enantiomeric purity.

Scheme I

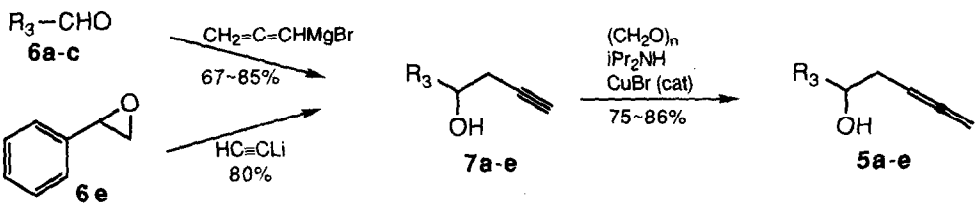


As outlined in Scheme II, we have employed two general synthetic methods for the preparation of the requisite starting β-allenic alcohols (**5a-i**).[6,7] In Method A the starting materials (**5a-e**) were readily available (75~86%) by the one-carbon homologation of propargylic alcohols (**7a-e**) by the procedure of Crabbé.[8] The latter alcohols were prepared either by addition

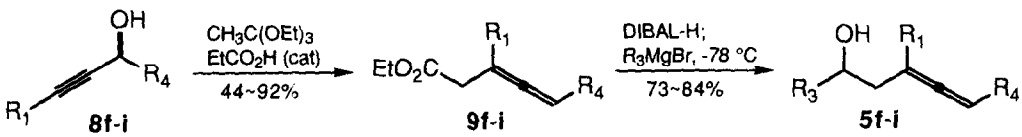
of allenylmagnesium bromide[9] to appropriate aldehydes (**6a-c**) or by treatment of lithium acetylide-ethylenediamine complex with styrene oxide. Enantiomerically pure β-allenic alcohols (**5c&d**) were thus easily prepared from (*S*)-2-benzyloxymethoxypropionaldehyde (**6c**).[10] Method (B) starts with the ester-Claisen rearrangement of propargyl alcohols (**8f-i**).[11] DIBAL-H reduction (-78 °C) of the resulting allenic esters (**9f-i**), followed by in situ treatment with an appropriate Grignard reagent gave the desired β-allenic alcohols (**5f-i**) in good overall yield.

Scheme II

Method (A)



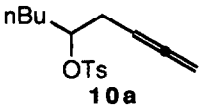
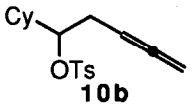
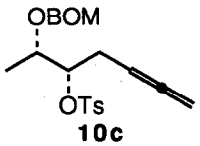
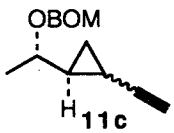
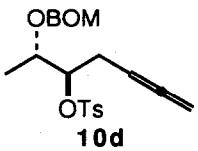
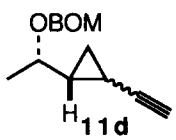
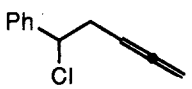
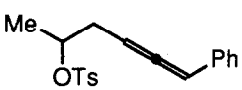
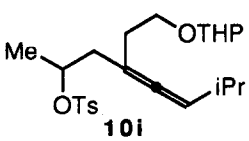
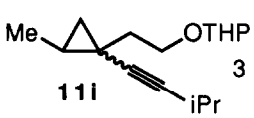
Method (B)



(a) R_3= nBu. (b) R_3= Cy. (c) R_3= (*S*)-CH_3CH(OBOM)-*syn*. (d) R_3= (*S,R*)-CH_3CH(OBOM)-*anti*.
(e) R_3= Ph. (f) R_1= H, R_3= Me, R_4= Ph. (g) R_1= H, R_3= nBu, R_4= Ph. (h) R_1= H, R_3= nBu, R_4= Cy.
(i) R_1= CH_2CH_2OTHP, R_3= nBu, R_4= iPr.

The starting β-allenic alcohols (**5a-i**) were converted smoothly (58~81% yield) into the corresponding tosylates (**10a-d & f-i**) by the action of *p*-toluenesulfonyl chloride under standard conditions, except **5e** wherein chloride **10e** was obtained. As shown in the following Table, upon treatment of LDA at -78 or 0 °C, the tosylates or chloride underwent a facile, although stereorandom, cyclization to furnish the corresponding alkynylcyclopropanes (**11a-i**) in good yield. In the case of β-allenic tosylate **10h**, treatment with LDA did not give rise to an appreciable amount of cyclopropane **11h**, but the desired cyclization was accomplished by the use of nBuLi (entry 8). The cyclization is thought to take place by the initial deprotonation of the distal allenic proton and subsequent intramolecular S_N2 displacement.[12] Hence the cyclopropane formation is expected to proceed with inversion of configuration at the carbon bearing the leaving group. Since the starting β-allene alcohols can be readily available in very high enantiomeric purity (i.e., entries 3 and 4),[13] the present method provides an easy entry to chiral, nonracemic cyclopropanes possessing an alkyne side-chain useful for further elaboration.[5]

Further work for the enantioselective synthesis of structurally more complex cyclopropanes will be reported in due course.

Entry	starting allenes	yield	products	ratio
1	 **10a**	*a* 64%	 **11a**	2 : 1
2	 **10b**	*a* 75%	 **11b**	1 : 1
3	 **10c**	*a* 91%	 **11c**	2 : 1
4	 **10d**	*a* 74%	 **11d**	4 : 3
5	 **10e**	*a* 82%	 **11e**	1 : 1
6	 **10f**	*a* 59%	 **11f**	1 : 1
7	 **10g**: R_4 = Ph;	*a* 80%	 **11g**: R_4 = Ph;	1 : 1
8	**10h**: R_4 = Cy.	*b* 75%	**11h**: R_4 = Cy.	1 : 1
9	 **10i**	*a* 78%	 **11i**	3 : 1

reagents: (a) 3~5 equiv LDA, THF, -78 or 0 °C, 30 min; (b) 2 equiv nBuLi, THF, -78 °C, 1h.

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References and Footnotes

1. (a) Current address: Department of Chemistry, University of Alabama, Tuscaloosa, AL 35487. Recipient of an NIH Research Career Development Award, 1990-1995 (GM00575). (b) On leave (June 1990~May 1991) from Sunkyong Industries, S. Korea. (c) Undergraduate Research Participant (1989~1990).

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