CHEMISTRY LETTERS, pp. 255 - 258, 1984.

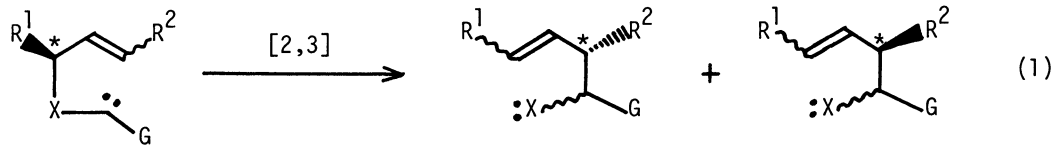
1,4-CHIRALITY TRANSFER VIA THE [2,3]-WITTIG REARRANGEMENT OF CHIRAL ALLYLIC PROPARGYL ETHER SYSTEM. A NEW, PRACTICAL ENTRY TO CHIRAL PROPARGYLIC ALCOHOLS

Noboru SAYO, Fumiyuki SHIRAI, and Takeshi NAKAI*

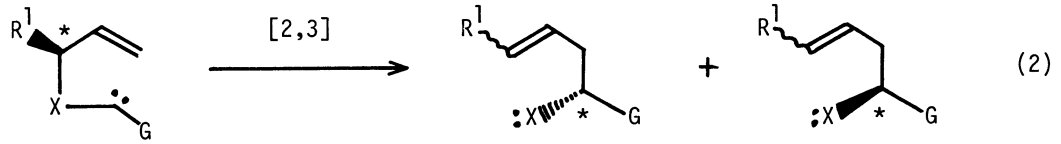
Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152

The [2,3]-Wittig rearrangement of enantiomerically-enriched α-methylallyl propargyl ethers provides a high degree (*ca.* 90%) of 1,4-chirality transfer, together with 95-98% of (E)-selectivity. The observed sense of 1,4-chirality transfer is discussed on mechanistic grounds.

One of the most valuable stereochemical features of sigmatropic rearrangement is the ability to specifically transmit the substrate chirality to the newly created chiral center(s) in the product. In principle, the [2,3]-sigmatropic rearrangement is capable of the two distinct types of chirality transfer, *i.e.*, 1,3-chirality transfer along the allylic array (Eq. 1) and 1,4-chirality transfer across the newly formed σ-bond (Eq. 2). While the 1,3-chirality transfer has been studied in a few variants,[1] the 1,4-chirality transfer has never been explored.



(1)

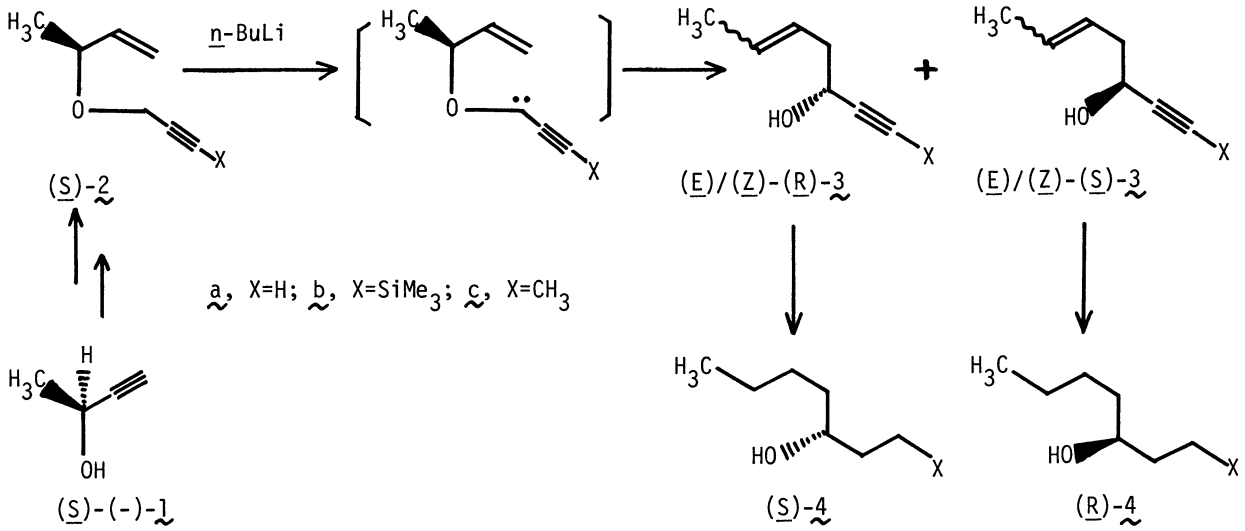


(2)

In an effort to develop the [2,3]-Wittig sigmatropic rearrangement into a new, basic strategy for acyclic stereocontrol,[2] we initiated to investigate the 1,4-chirality transfer via the [2,3]-Wittig process of chiral allylic ethers (X=O). Since this type of "self-immolative"[3] asymmetric synthesis associates with both the enantioselectivity over the newly created chiral center and the stereoselectivity over the newly formed double bond, the success depends critically upon the proper selection of the substituents G and R. Herein we wish to report our observations on the sense and degree of 1,4-chirality transfer in the [2,3]-Wittig rearrangement of the three enantiomerically-enriched α-methylallyl propargyl ethers (2)[4] (Scheme 1).

The chiral substrates (S)-2 were derived from an optically-resolved[5] alcohol (S)-1 via the conventional sequence.[6] The carbanion rearrangement of 2 was carried out according to the standard procedure (n-BuLi, THF, -85—-65 °C). We found that the rearrangement afforded a stereoisomeric mixture of the propargylic alcohol 3 in 90-95% isolated yields.[7] The geometric ratio (E/Z) for 3 was determined by combination of IR and GLC. The enantiomeric excess of 3 regardless of the olefin geometry was determined by ^{19}F NMR analysis of the respective MTPA-ester (Mosher method).[8] In order to assign the absolute configuration of the major stereoisomer of 3, the rearrangement product (3) was hydrogenated (H_2, Raney nickel, EtOH) to 4[9] and the $[\alpha]_D$-value

Scheme 1.



for 4 was compared with the literature value: $[\alpha]_D$ +8.0 (EtOH) for (S)-4a[10] and +0.27 (EtOH) for (S)-4c.[11] In the case of 2b (X=$SiMe_3$), the product stereochemistry was determined after conversion of 3b to 3a via protodesilylation (CsF, aqueous methanol, 50 °C). Table 1 summarizes the stereochemical outcomes including the calculated degree of 1,4-chirality transfer.

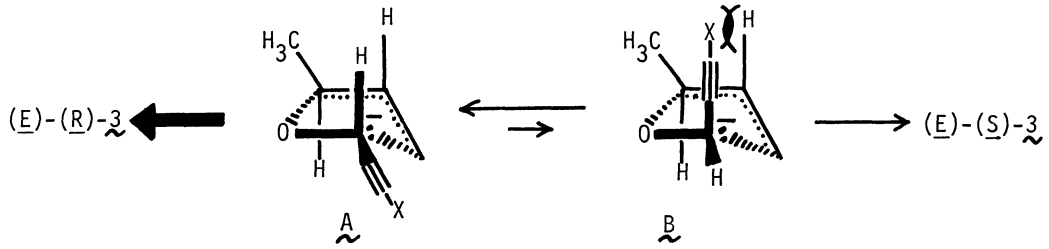
Inspection of the data in Table 1 reveals important points concerning the sense and degree of 1,4-chirality transfer via the present [2,3]-Wittig variants. (1) The (S)-configuration in the substrate is specifically transformed to the (E)-(R)-configuration in the product during all the rearrangements examined. (2) In the rearrangements of 2a and 2c, the degree of chirality transfer is as high as *ca.* 90%, together with 95-98% of (E)-selectivity. (3) The introduction of the silyl group leads to a slightly lower degree of chirality transfer and (E)-selectivity (run 3).[12] Although the specific effect of the added silyl group on the stereoselectivity has no straightforward explanations at present, the observed sense of 1,4-chirality transfer can be visualized as follows on the basis of our own transition-state model.[13]

Table 1. The Stereochemical Outcomes in the [2,3]-Wittig Rearrangements of (S)-2

Run	Substrate (% ee)[a]	3E : 3Z[b]	% ee of 3[c]	$[\alpha]_D$ for 4 (c, EtOH)[d]	Config. of major 3[e]	1,4-Cirality transfer, %[f]
1	(S)-2a, X=H (90)	98 : 2	(84)[g]	+6.47°(1.16)	R	93
2	(S)-2a, X=H (94)	95 : 5	86		R [h]	92
3	(S)-2b, X=$SiMe_3$ (94)	93 : 7	76 [i]		R [h]	81
4	(S)-2c, X=CH_3 (90)	97 : 3	80	+0.20°(1.02)	R	89

a) Refers to % ee of the starting (S)-1 used for the preparation, as judged from the highest rotation value: $[\alpha]_D^{22}$-51.8°(c 3.8, dioxane): L.-I. Olsson and A. Claeson, *Acta Chem. Scand.*, B31, 614 (1977). b) Determined by GLC analysis (PEG 20M, 150 °C: 3a, t_R=19.5 min (E) and 22.7 min (Z); 3c, t_R=30.4 min (E) and 35.0 min (Z). c) Determined by Mosher method (see the text). Note that the values are regardless of the olefin geometry (see Ref. 8). d) Measured at 25 °C (c=g/100 ml). e) Based on reported configuration of (+)-(S)-4 (see the text). Note that (S)-4 is correlated to (R)-3 due to a priority change. f) Stands for % ee of 3 (regardless of the olefin geometry) relative to % ee of 2. g) Determined through comparison of the observed $[\alpha]_D$-value for 4a with the reported value (+8.0°). h) Assigned by similarity in chemical shifts in ^{19}F NMR of the MTPA-ester. The CF_3 singlet of the major enantiomer appeared at a higher field than that of the minor one. i) Refers to % ee of 3a derived from 3b (see the text).

Of the two possible transition-state conformations leading to the (E)-geometry,[14] the conformation A leading to the (R)-configuration is sterically more favorable than the conformation B since the latter suffers the large pseudo-1,3-diaxial repulsion as indicated in the formula.



In summary, this work demonstrates that the [2,3]-Wittig rearrangement of enantiomerically-enriched allyl propargyl ether systems such as 2a and 2c provides a new, practical method (starting from chiral propargylic alcohols) for the highly enantiospecific synthesis of a particular type of propargylic alcohols such as 3a and 3c. The rearrangement products possess the unique multi-functionality suitable for further synthetic elaborations, thus making the present methodology potentially useful for asymmetric synthesis of several natural products. We are now investigating not only the synthetic utility of the chiral propargylic alcohols thus obtained but also the 1,4-chirality transfer via different [2,3]-Wittig variants.

This research was generously supported by the Kurata Foundation and the Grant-in-Aid for Special Project Research from the Ministry of Education, Science and Culture.

References

1) N. Sayo, Y. Kimura, and T. Nakai, *Tetrahedron Lett.*, 23, 3931 (1982); K.-K. Chan and G. Saucy, *J. Org. Chem.*, 42, 3828 (1977); J. G. Miller, W. Kurz, K. G. Untch, and G. Stork, *J. Am. Chem. Soc.*, 96, 6774 (1974); J. E. Baldwin and J. E. Patrick, *ibid.*, 93, 3556 (1971).

2) For a preceding paper on this series, see: N. Sayo, K. Azuma, K. Mikami, and T. Nakai, *Tetrahedron Lett.*, in press. For a review on acyclic stereocontrol via sigmatropic rearrangements, see: T. Nakai, K. Mikami, and N. Sayo, *J. Synth. Org. Chem., Jpn.*, 41, 100 (1983).

3) For the terminology, see: K. Mislow, "Introduction to Stereochemistry," Benjamin, New York (1965), p. 131.

4) The main reason why we have now selected the ethynyl groups as the key G is that the use of these groups provides an exceptionally high diastereoselectivity in the [2,3]-Wittig process of the (E)- or (Z)-crotyl ethers: K. Mikami, K. Azuma, and T. Nakai, *Chem. Lett.*, 1983, 1379.

5) R. Weidman, A. Schoofs, and A. Horeau, *Bull. Soc. Chim. Fr.*, 1976, 645.

6) Ether 2a was prepared in 85% yield via reaction of propargyl bromide with (S)-α-methylallyl alcohol derived from (S)-1: bp 114-115 °C. Ether 2b and 2c were obtained from (S)-2a in 80-90% via treatment with EtMgBr followed by Me_3SiCl and CH_3I, respectively: 2a, bp 67-68 °C/8 mmHg; 2c, bp 62-63 °C/20 mmHg.

7) 3a, bp 75-85 °C/8 mmHg; 3c was purified by column chromatography (silica gel, hexane/ether).

8) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 34, 2543 (1969): MTPA = (-)-α-methoxy-α-trifluoromethylphenylacetic acid. It should be noted that ^{19}F NMR of a MTPA-ester of chiral 3 (geometric mixture) showed only two ^{19}F signals for the enantiomeric pair (not for the geometric pair), as revealed by only two ^{19}F signals with the same intensity in the spectrum of a MTPA-ester of racemic 3 (geometric mixture).

9) 4a, bp 73-75 °C/14 mmHg; pure 4c was obtained by bulb-to-bulb distillation in vacuo.

10) R. I. Johnson and J. Kenyon, *J. Chem. Soc.*, 1932, 722.

11) P. A. Levene and A. L. Haller, *J. Biol. Chem.*, 83, 579 (1929).

12) This is somewhat surprising in view of the remarkable increase in erythro-selectivity by the introduction of TMS group in the [2,3]-Wittig process of the (Z)-crotyl propargyl ether system.[4] However, this is not entirely unexpected in view of the great decrease in threo-selectivity observed with the (E)-crotyl counterpart.[4]

13) For a detailed discussion of the transition-state geometry for [2,3]-Wittig rearrangement, see: K. Mikami, Y. Kimura, N. Kishi, and T. Nakai, *J. Org. Chem.*, 48, 279 (1983).

14) These exo-conformations are sterically more favorable than the endo-counterparts leading to the (Z)-geometry, which place the methyl group at the endo-orientation.

(Received November 28, 1983)