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ACYCLIC ASYMMETRIC INDUCTION WITH CARBON-CARBON BOND FORMATION

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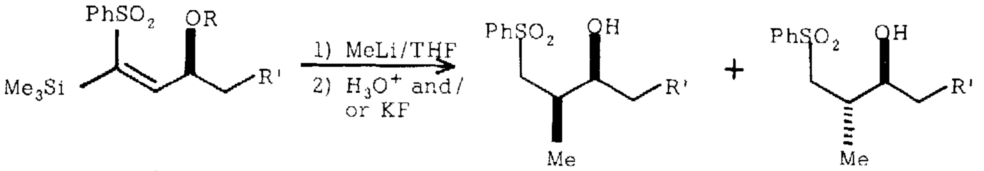
The acyclic asymmetric induction is described which involves heteroconjugate addition of MeLi to α-hydroxy hetero-olefins and concomitant intramolecular silicon-migration to produce α,α-sulfonyl-dianion of the threo adduct being of utility for the second C-C bond formation in one pot. It also contains the first chemical proof of the regiochemical assignment to the hetero-olefins.

Much effort has recently been made with great progress for developing new methodologies for acyclic asymmetric induction.[1] We have recently developed the heteroconjugate addition[2] useful for construction of threo isomers with carbon-carbon bond formation as an important step aiming at synthesis of a macrolide.[3] The asymmetric induction, however, became impractically worse when applied to the more functionalized molecules. This was due to the principal chelation effect which became diverse by the side effect with an alternative etherial moiety if it was present in the molecule. We describe here the properties and scopes of this asymmetric induction surmounting those difficulties and being of general utility for macrolide syntheses.[4]

Scope of this 1,2-asymmetric induction was examined by addition of methyllithium to such hetero-olefins conjugated with silicon and sulfonyl-sulfur atoms as 1, each of which has an allylic alkoxide as an original asymmetric center. After taking the protective groups off the adducts, the ratios of 2 and 3 were analized by nmr[5] and the results are summarized in Table 1. The simplest hetero-olefin as 1a was added by 1 eq. of methyllithium at -78°C to give 97%[6] threo adduct [2a] owing to the allylic MEM-oxy ($CH_3OCH_2CH_2OCH_2O$-) group which functioned as an open-chain crown ether as was previously reported by us.[3] However, the ratio 2/3 was diminished to 90/10 in the case of 1d due to the side chelation effect by methoxymethyloxy group in the same molecule. This was solved by the following manner. First, the threo-induction also took place even in the non-protected allylic hydroxy-hetero-olefin [1, R=H] by treatment with 2 eq. of methyllithium (see entry 2). Secondly, the results were even better than in the MEM-oxy cases even if the etherial function was present. Thus, in entries 2,6,7 and 8 a strong coordination of lithium cation



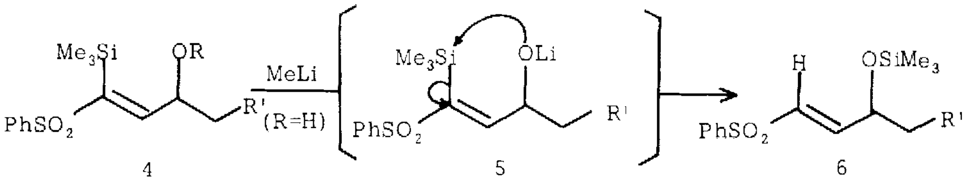
1 2 3

Table 1

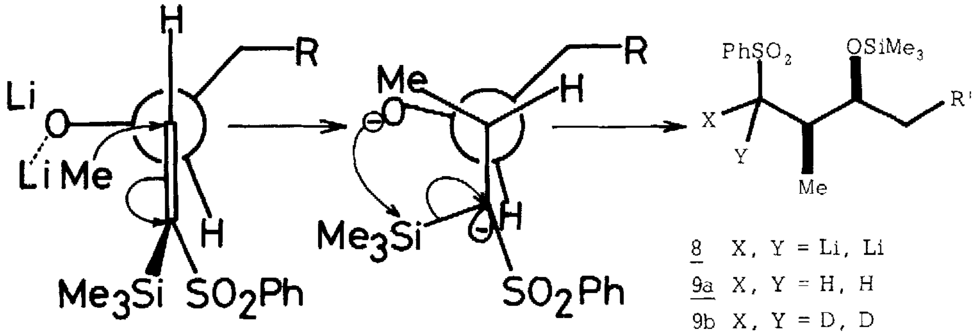
Entry	Compd.	R	R'	Electrophile	React. Temp. (°C)	React. Time (min)	2 / 3 threo / erythro	Yield
1	1a	MEM	CH_2Ph	MeLi	-78	10	97 / 3	95
2	1b	H	CH_2Ph	MeLi	-78	10	>99 / <1*	85
3	1b	H	CH_2Ph	MeMgBr	18	720	80 / 20	23
4	1c	$SiMe_2Bu^t$	CH_2Ph	MeLi	-40	20	95 / 5**	52
5	1d	MEM	$C{\equiv}CCH_2OCH_2OMe$	MeLi	-78	15	90 / 10	78
6	1e	H	$C{\equiv}CCH_2OTHP$	MeLi	-78	20	97 / 3	90
7	1f	H	$C{\equiv}CCH_2OH$	MeLi	-78	60	>99 / <1*	65
8	1g	H	$(CH_2)_3OCH_2OMe$	MeLi	-78	20	>99 / <1*	95

* erythro isomers were not detectable by nmr

** determined only by pmr (±5 %)



4 5 6



7

8 X, Y = Li, Li

9a X, Y = H, H

9b X, Y = D, D

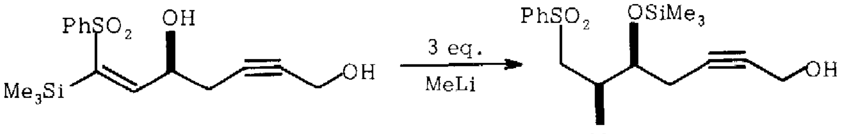
9c X, Y = H, allyl

Fig. 1

with the allylic alkoxide oxygen instead of the polyetherial MEM-oxy moiety fixed the methyllithium on one side of the olefin to eventuate in that such a remarkable acyclic asymmetric induction occurred pseudo-intramolecularly to form a new carbon-carbon bond in threo orientation (see Fig. 1). In all cases in Table 1, the threo induction was predominant or exclusive, although the diastereoselection is slightly affected by the nature of R and R' groups. The primarily significant factor for the selection was R which worked better in the order of H $\geqq$ MEM > SiMe$_2$Bu^t by comparison of entries 1,2 with 4 or entries 5 with 6. In cases of Grignard reagent instead of MeLi (entry 3) and silyl ether as bulky protective group (entry 4), no addition took place at -78°C. The polyetherial group, MEM, played an important role when no other etherial functional group existed in R'. However, MEM became less important relative to the free hydroxy cases (R=H) when etherial moiety like entry 5 was present. Among all, free hydroxy group showed the best asymmetric induction.

E isomers of the hetero-olefins 4, on the other hand, displayed a different reactivity from that of Z isomers when they had a free hydroxy group instead of the MEM-oxy group. When 4 (R=H, R'=CH$_2$Ph) was treated with 2 eq. of MeLi at -78°C for 10 min, for example, it was converted into TMS-oxy-trans-sulfone (6, R'=CH$_2$Ph) in 40 % yield with little methyl adduct. However, both of Z and E isomers of MEM-protected hetero-olefins (1 and 4, R=MEM) showed no such side reaction at all. This means that the mechanism involved a faster intramolecular silicon-transfer (like 5) than the addition, which further means the first chemical proof of the regio-structure of E and Z hetero-olefins.[7]

When the free hydroxy Z-hetero-olefins [1b, 1e, 1f and 1g] were treated with 2 eq. of MeLi, the products were largely 2-Me-3-TMSoxy-sulfones (such as 9a) which formed via transfer of Si from C to O atoms (see 7). This mechanism was confirmed by the fact that 1] trapping of 8 with D$_2$O at -78°C afforded α,α-dideuterosulfone 9b (X=Y=D, R'=CH$_2$Ph) and that 2] the diol 1f, by treatment with 3 eq. of MeLi gave 10, whose TMS group was located selectively on the 3-alkoxy oxygen[8] (not on the terminal oxygen) through intra-molecular five membered process as 7. These facts further implied a possibility of a "one-pot" carbon chain elongation using the intermediate dianion (8); in fact it afforded 9c (X,Y=H, allyl; R'=CH$_2$Ph) by treatment with allyl bromide at 0°C.



1f

10

It should be noted that these Z-hetero-olefins were preparable as the major products from the corresponding α-alkoxy aldehydes by condensation with lithium bis(trimethylsilyl)-benzenethiomethylide.[2] Thus, the application of this asymmetric induction could be anticipated for syntheses of optically active alcohols such as 2 as starting from sugars. One of the examples may appear in the following paper.

ACKNOWLEDGEMENT

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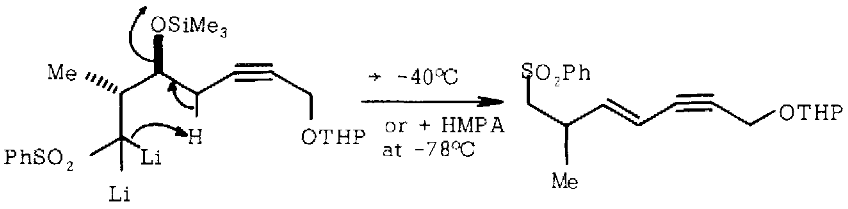
2. M. Isobe, M. Kitamura, T. Goto, Chem. Lett., 331 (1980).
3. M. Isobe, M. Kitamura, T. Goto, Tetra. Lett., 3465 (1979).
4. A part of this work was presented in 1st Int. Kyoto Conference on New Aspects of Organic Chemistry, Kyoto (1979, Dec.).
5. Assignments of the diastereoisomers were made by direct comparison of the product 2 with the authentic sample (see Ref. 3) and also by the analogical cmr-chemical shifts of methyl signals which appeared at δ 14.0±0.2 ppm for threo isomers (2) but did at δ 17.2±0.2 ppm for erythro ones (3). The latters were observed on the 50/50 mixtures of 2 and 3 which were prepared by Jones oxidation of the alcohols (2) followed by the reduction with sodium borohydride.
6. This number was initially reported as >99%, but repetition of the same reaction revealed that it should be corrected to be 97%.
7. This assignment is coincident with the similar cases reported by us (Ref. 2) and by B. T. Grobel, D. Seebach [Chem. Ber., 110, 852 (1977)]. In the pmr spectra of 1 and 4; olefinic H's of 1 (trans to sulfonyl) appeared at δ 6.3±0.3 ppm but the H's of 4 (cis to sulfonyl) did at δ 7.2±0.1 ppm.
8. An elimination of the silyloxy group occurred at higher temperatures than -78°C or by addition of HMPA to the reaction mixture even at -78°C to form the following product.



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