Pure & Appl. Chem., Vol. 69, No. 3, pp. 595–600, 1997.
Printed in Great Britain.
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Asymmetric [2,3]-Wittig rearrangement as a general tool for asymmetric synthesis

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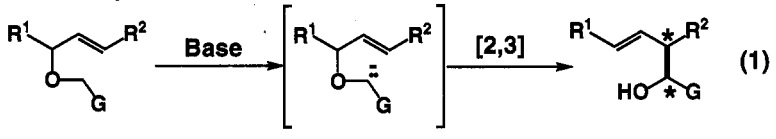
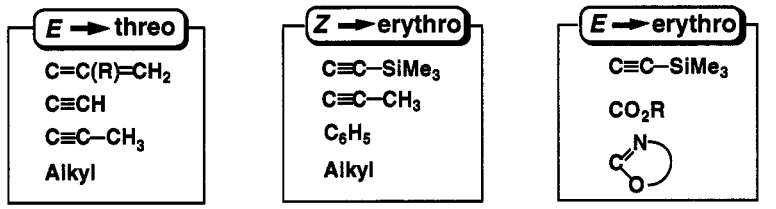
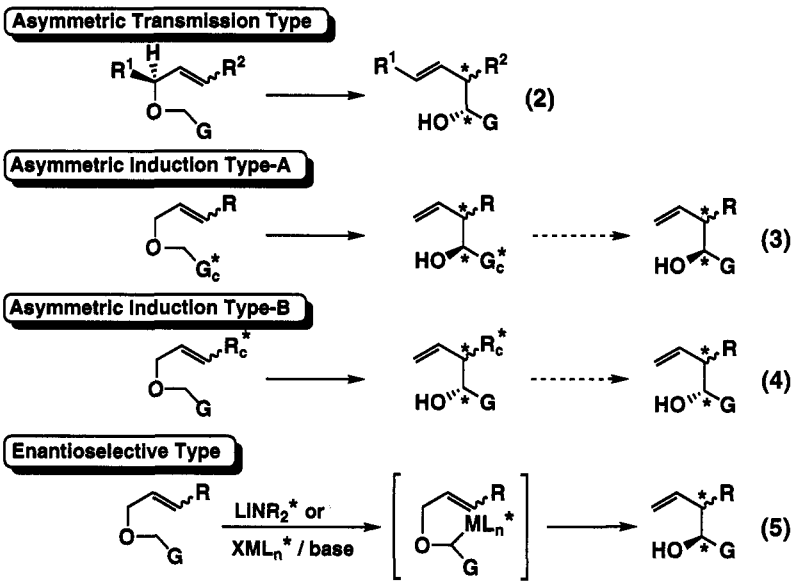
Abstract: Recent advances in the asymmetric [2,3]-Wittig rearrangement as a general tool for asymmetric synthesis of homoallylic alcohols are described. First, the synthetic utilities of the asymmetric transmission type and the two asymmetric induction types are demonstrated, including applications in asymmetric syntheses of natural products and steroid side chains. Second, some examples are presented of the enantioselective versions involving a chiral ligand-bound boron enolate and organolithium as the migrating terminus. Finally, the mechanistic grounds of the asymmetric versions are discussed on the basis of the stereochemical analyses of the asymmetric version involving an enantiomerically-defined carbanion terminus.

The [2,3]-Wittig rearrangement is a special class of [2,3]-sigmatropic rearrangement which involves an α-oxy carbanion as the migrating terminus to afford various types of homoallylic alcohols. As can be seen in the general formula (eq. 1), this type of carbanion rearrangement possesses synthetically valuable features, including (a) the regiospecific carbon-carbon bond formation with allylic transposition of the oxygen function, (b) the stereoselective formation of a new olefinic bond, and (c) the stereoselective creation of vicinal chiral centers. Thus, the [2,3]-Wittig rearrangement currently enjoys widespread application in many facets of organic synthesis, particularly in the context of acyclic stereocontrol and natural product synthesis (ref. 1). The most significant feature is its ability of efficient diastereocontrol over the newly-created chiral centers through the proper choice of the combination of G group and substrate geometry. Some of the highly diastereoselective variants thus developed are shown below which provide a higher than 95% of either *threo* or *erythro* diastereoselectivity (refs.1, 2).

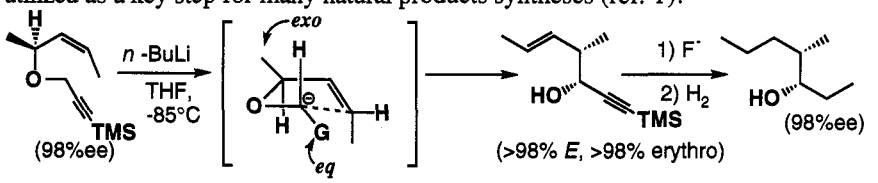




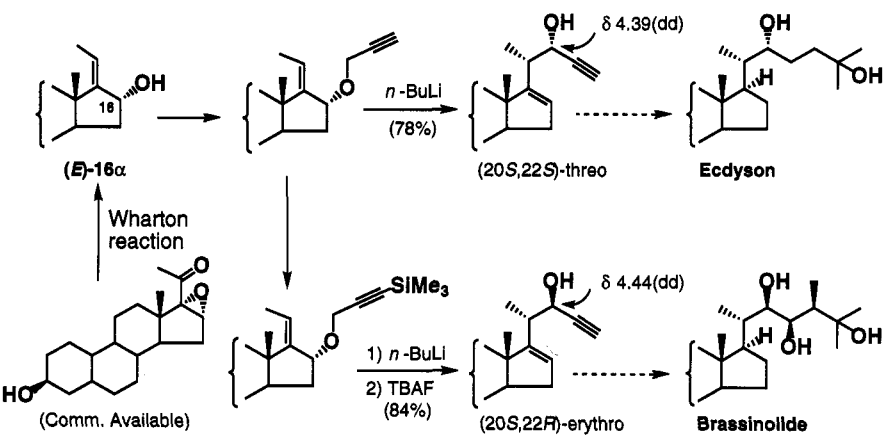
The present article focuses on the great potentials of several *asymmetric versions* of the [2,3]-Wittig rearrangement as general tools for asymmetric synthesis. The asymmetric versions outlined herein include the "asymmetric transmission type" (eq. 2), the "asymmetric induction type-A" (eq. 3) and "type-B" (eq. 4), and the "enantioselective type" (eq. 5), depending upon the location of the stereogenic center involved. Note that, in principle, all the asymmetric versions allow for the concurrent control of absolute and relative stereochemistry to provide highly diastereo- *and* enantio-enriched homoallylic alcohols.



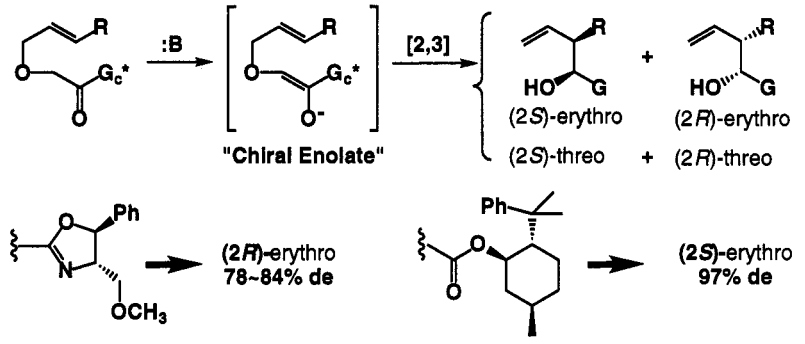
Asymmetric Transmission Type. As can be seen in eq. 2, this type of asymmetric version destroys the original chirality while simultaneously creating new ones. Guided by the transition state model advanced for diastereoselection (ref. 2), one can readily predict the absolute and relative stereochemistry of the product from the three variables in the substrate: the absolute configuration, the double bond geometry, and the nature of G group. The first success was made in the (*Z*-to-*erythro*)-selective variant shown below, where the substrate chirality is completely and specifically transmitted to the two new chiral centers, as predicted from the specific transition state indicated below, to eventually afford the insect pheromone of the same %ee as that of the substrate (ref. 3). This asymmetric transmission technology is widely applicable to both acyclic and cyclic substrate with considerable stereopredictability and, indeed, has been widely and increasingly utilized as a key step for many natural products syntheses (ref. 1).



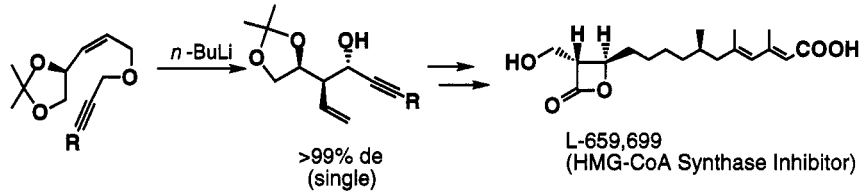
Perhaps one of the most remarkable applications is the highly stereocontrolled synthesis of either (22*S*)- or (22*R*)-steroid side-chain from the single precursor, easily derived from the commercially available epoxypregnenolone, where the dianion rearrangement affords (20*S*, 22*S*)-side chain (ecdyson-type) as a single stereoisomer, whereas the introduction of the silyl group induces the reversal of diastereoselection to give (20*S*, 22*R*)-side chain (brassinolide-type), again, as a single stereoisomer (ref. 4).



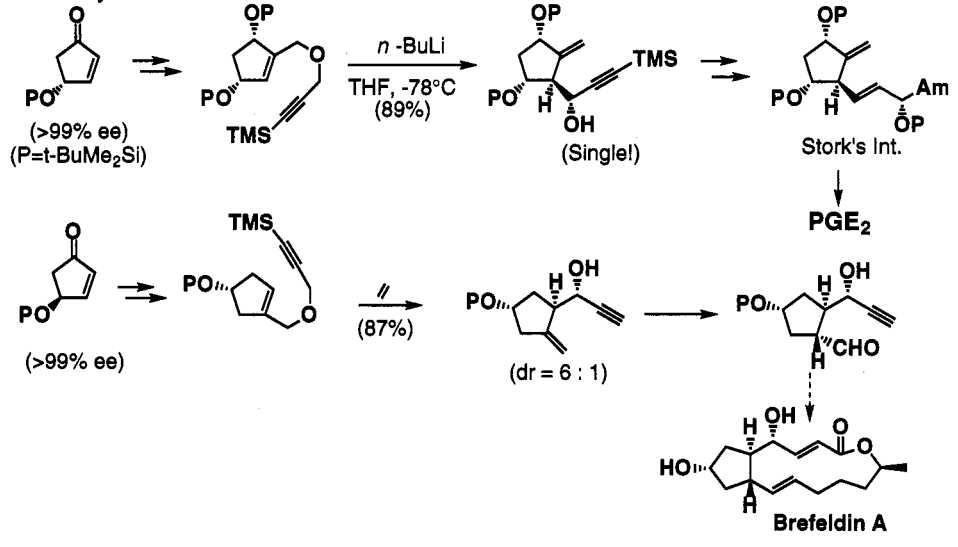
Asymmetric Induction Type-A. As can be imagined from eq. 3, the key to success in this type of asymmetric version is the proper choice of the chiral substituent (Gc*). Well studied thus far are the rearrangements involving various *chiral* enolate termini. The first example reported employs the chiral 2-oxazoline ring (Meyers' chiral auxiliary) as the Gc* to provide a reasonably high level of diastereofacial selection and *erythro* selection (ref. 5). Later, a much higher level of diastereofacial selection was attained by using the chiral 8-phenylmenthol-derived substrate (ref. 6). Thus, this type of asymmetric "enolate [2,3]-Wittig" rearrangement provides a powerful tool for asymmetric synthesis of a variety of α-hydroxy β-alkyl carboxylic acid derivatives, an important class of intermediates for natural product synthesis.



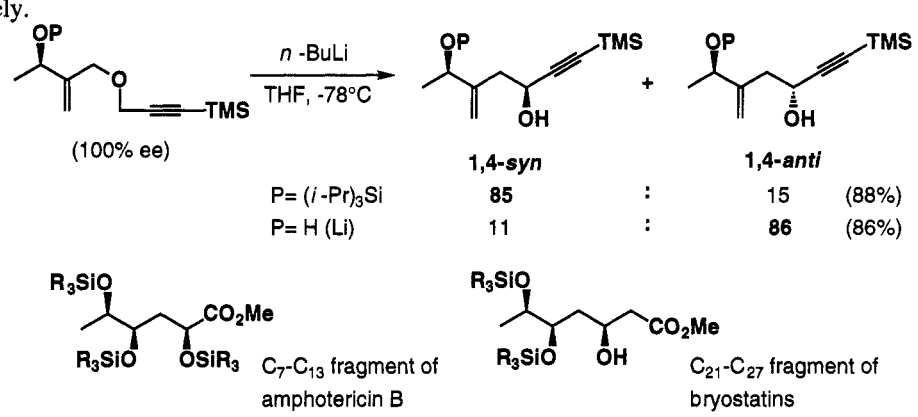
Asymmetric Induction Type-B. As can be seen in eq. 4, this type of asymmetric version involves both the diasterofacial selection between the chirality existing in the chiral γ-substituent (Rc*) and a newly-created chiral center and the simple diastereoselection between the two new chiral centers. The first successful example is shown below, where essentially the single stereoisomer (among four possible stereoisomers) is formed (ref. 7). Later, this enatio-pure product was demonstrated to serve as a useful chiral building block for the total synthesis of the HMG-CoA synthase inhibitor (ref. 8).



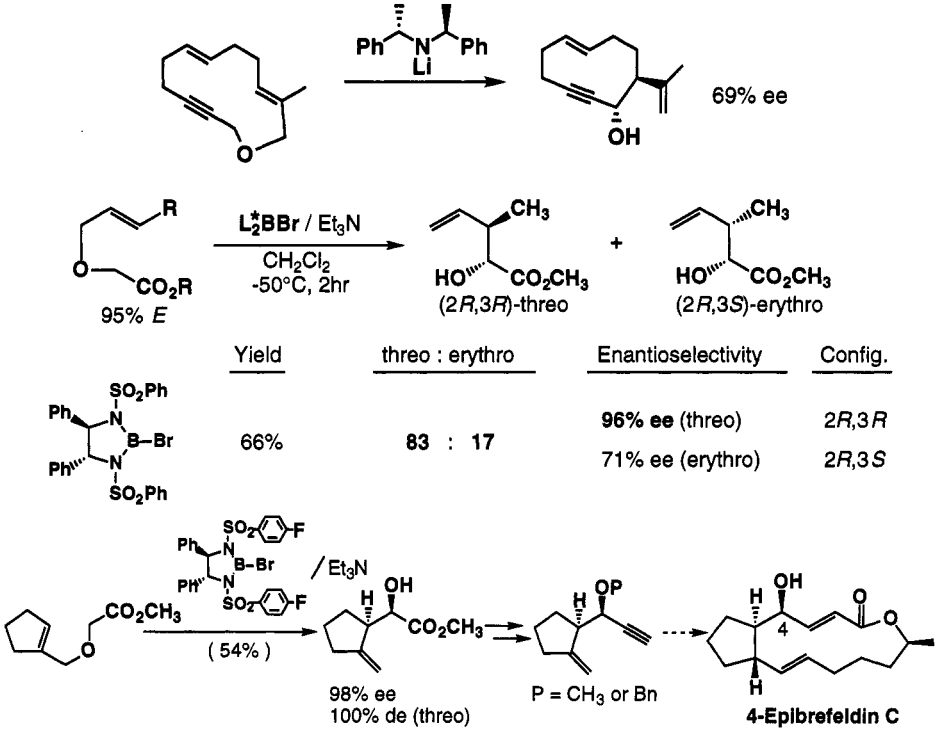
More recently, this asymmetric induction protocol has been successfully applied to cyclic systems with efficient stereocontrol over the three contiguous chiral centers. Illustrated below are the [2,3]-Wittig-mediated synthetic routes to prostaglandin E_2 (ref. 9) and the brefeldin A key intermediate (ref. 10); the rearrangement product was obtained as the single stereoisomer in the former, but with a slightly lower diastereoselectivity in the latter.



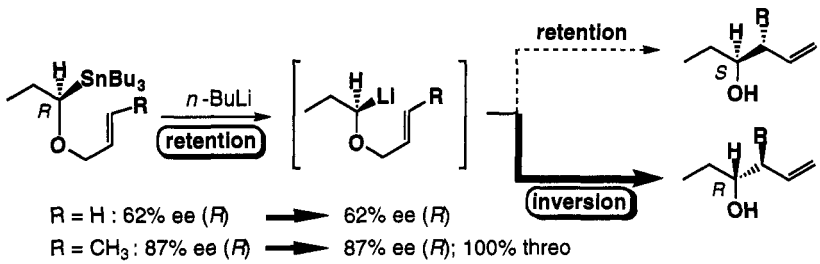
This type of asymmetric induction protocol can also be applied to systems with a chiral substituent at the β-position (instead of the γ-position) to accomplish the otherwise difficult 1,4-remote stereocontrol as depicted below (ref. 11). Significantly enough, the rearrangement proceeds with a high degree of either 1,4-*syn* or 1,4-*anti* selection by virtue of the proper choice of the alkoxy group (OP); the 1,4-*syn* and 1,4-*anti* products were converted into the C_7-C_{13} fragment of amphotericin B and the C_{21}-C_{27} fragment of bryostatins, respectively.



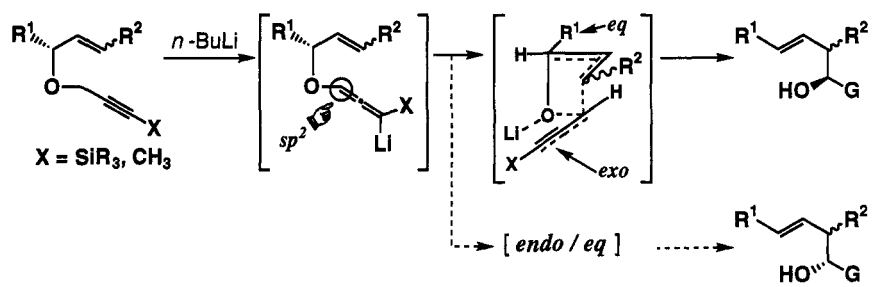
Enantioselective Type. As can be seen in eq. 5, this type of asymmetric version should involve an *enantioselective* generation of the chiral terminus from an *achiral* substrate with a chiral *nonracemic* base or chiral ligand-bound metal reagent. Thus this type of enantioselective version is synthetically more valuable than the diastereoselective versions described above. The first success was achieved by Marshall's group in the ring-contracting rearrangement of the 13-membered cyclic ether with the chiral lithium amide base (ref. 12). However, no appreciable levels of %ee have been observed in the rearrangements of acyclic substrates with the same chiral amide base (refs. 12, 13)). Recently, we developed the first enantioselective version of the ester enolate [2,3]-Wittig rearrangement which involves a chiral boron enolate with a chiral bis-sulfonamide as the controller ligand to provide a high %ee, along with a high *threo* selectivity (ref. 14). Later, the chiral boron enolate methodology has been applied to the enantioselective synthesis of the 4-epibrefeldin C intermediate. (ref. 14b).



Configurationally Defined Carbanion Type: Relevance to Mechanisms for Stereocontrol via Asymmetric [2,3]-Wittig Rearrangement. Since all the asymmetric [2,3]-Wittig versions described so far involve a chiral carbanionic terminus, the fundamental problem encountered, which concerned the steric course, is inversion vs. retention at the lithium-bearing terminus, both of which are symmetry-allowed. That has been the subject of controversy. Conflicting conclusions have been drawn from the theoretical calculations (ref. 15). Recently, the experimental evidence in support of the inversion course has been accumulated (ref. 16). The most clear-cut evidence has been provided from our observation that the transmetallative rearrangement of the enantiomerically-defined α-(allyloxy)alkylstannanes proceeds with complete inversion of configuration at the lithium-bearing terminus as shown below (ref. 17). More recently we have found that the rearrangement of an enantiomerically-defined α-(propargyloxy)alkylstannane also proceeds with complete inversion of configuration at the Li-bearing terminus (ref. 18).



The inversion stereochemistry thus proved immediately raises a fundamental question which concerns how to establish an essentially single configuration at the newly-created hydroxy chiral center, as actually observed, during the above-mentioned asymmetric transmission and induction processes, while the lithium-bearing terminus involved should be, more or less, an epimeric mixture. These rather conflicting observations lead us to suggest that, while the rearrangement involving a *configurationally stable* α-oxyalkyllithium terminus follows the "inversion principle," most of the deprotonation-induced asymmetric versions discussed thus far, which involve a *configurationally unstable* Li-bearing terminus, do not follow the "inversion principle," but instead proceed through a mechanism involving a sort of "dynamic kinetic resolution" between the two epimeric termini. Shown below is an extreme, possible mechanism where the migrating terminus concerned is essentially planar (achiral) and the absolute configuration of the new hydroxy chirality might be determined by the relative stability of the pericyclic transition states (*exo* vs. *endo*).



In summary, we have convincingly demonstrated the high potential and wide applicability of the asymmetric [2,3]-Wittig technology. Thus, the five different types of asymmetric versions of the [2,3]-Wittig rearrangement outlined herein provide versatile synthetic tools for various classes of highly diastereo- and enantio-enriched homoallylic alcohols and hence could find many more applications in asymmetric synthesis and chiral technology.

This work is the result of experimental and intellectual contributions by many co-workers who are listed in the references. The [2,3]-Wittig project has been supported over the years by the Grant-in-Aids for Scientific Research from the Ministry of Education, Science and Culture, Japan.

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