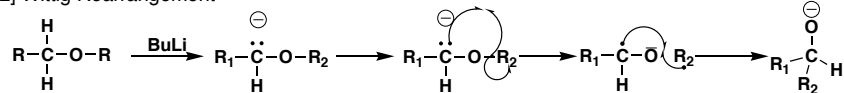
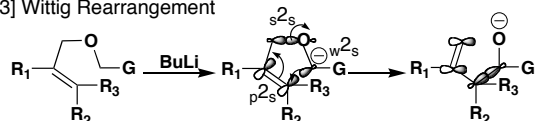


The Wittig Rearrangement

[1,2] Wittig Rearrangement



[2,3] Wittig Rearrangement



[1,2] Wittig Rearrangement:

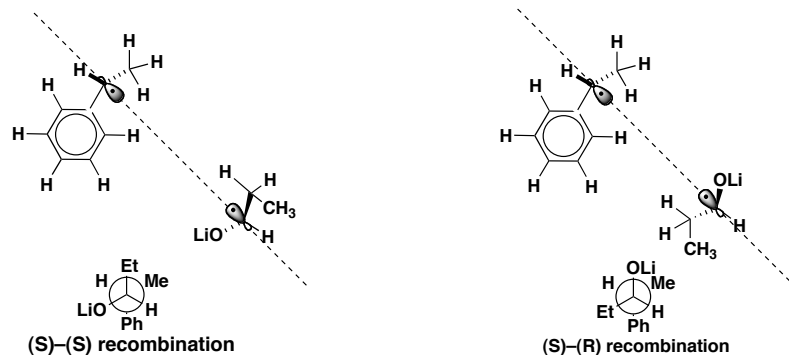
- [1,2] Wittig rearrangement, [2,3] Wittig rearrangement, and β -elimination compete in the same pot.
- Reaction success is related to the stability of generated radicals.
- Migratory aptitude is related to stability of generated radical.
- Rearrangement can exhibit stereoselectivity.

Enantioselectivities of radical recombination in the [1,2] Wittig Shift

Transmetalation of substituted stannylated benzylpropylethers

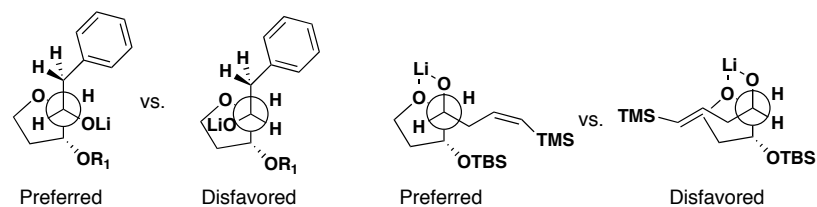
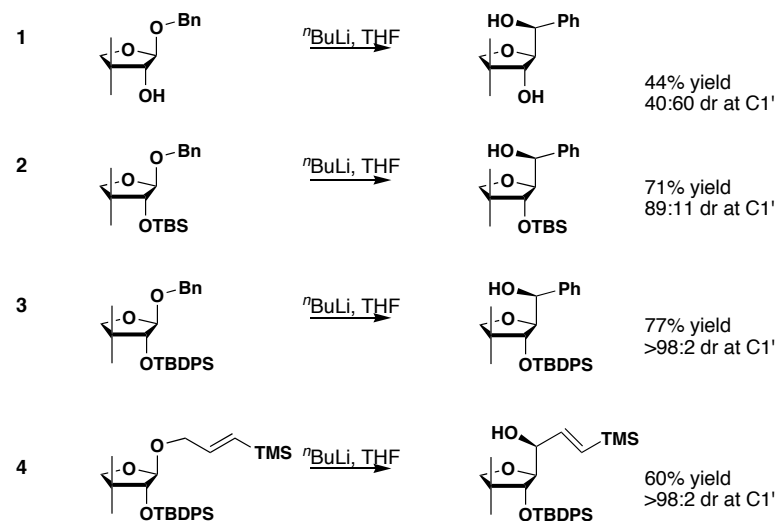
| Starting materials | Ph-CH(OH)-CH2-Et (R), (R) | Ph-CH(OH)-CH2-Et (S), (R) | Ph-CH(OH)-CH2-Et (S), (S) | Ph-CH(OH)-CH2-Et (R), (S) | Products following transmetalation |
|--------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------------|
| | 7 | 67 | 23 | 3 | |
| | 0 | 10 | 88 | 2 | |

Hypothesized transition states of radical recombination



Tomooka et al., *Tet. Lett.* **1993**, *34*, 8139-42

With substituted tetrahydrofuranethers, the recombination event is not as quick, and the radicals more readily sample different transition states.



Transition states available for ethers 1-3

Transition states available for ether 4

K. Tomooka, H. Yamamoto, T. Nakai, *Liebigs Ann./Recueil* **1997**, 1275

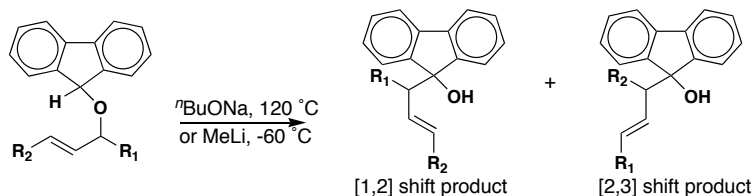
[1,2] Wittig Rearrangement Summary-

- The [1,2] Wittig Rearrangement proceeds through a radical dissociation/ recombination mechanism within a solvent shell.
- The [1,2] shift competes with β - elimination and pericyclic reactions such as the [2,3] Wittig and [1,4] shifts, giving poor to modest yields of product.
- Radical recombination proceeds with inversion of the alkoxide radical
- In some cases, chiral "memory" has been demonstrated within the [1,2] Wittig, relying on fast recombination to prevent scrambling

Gallagher

[2,3] Wittig Rearrangement

- The [2,3] Wittig Rearrangement is a sigmatropic rearrangement.
- Lower temperatures affords [2,3] rearrangement over advantageous [1,2] rearrangement.



Wittig, G. Döser, H. *Justus Liebigs Ann. Chem.* **1949**, 556, 192-205.

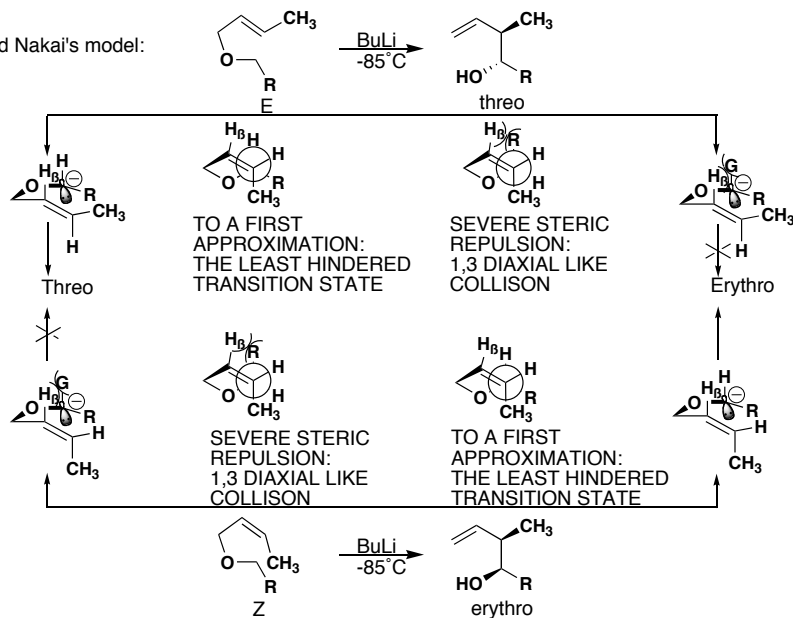
Regiochemistry of the [2,3] Wittig Rearrangement



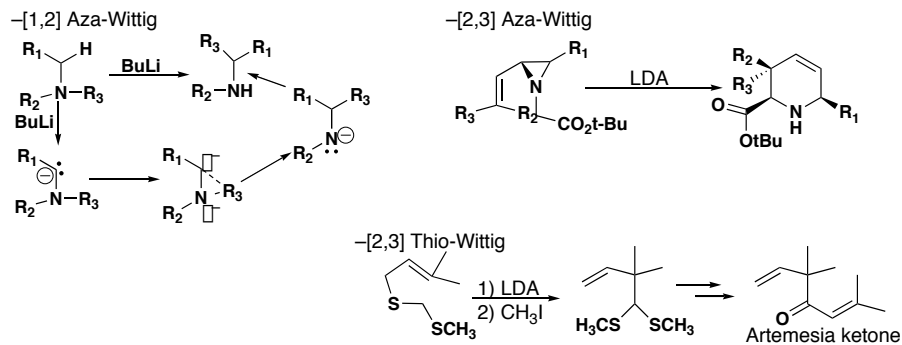
While a single transition state hypothesis has not fully explained the [2,3] Wittig shift, it is thought to adopt an envelope configuration:

1. Postulated to be involved in ylide [2,3] Wittig rearrangements
2. Most commonly assumed, classical configuration that is supported by calculation (Wu, Houk, Marshall, *J. Org. Chem.*, 55, 1421) and inversion at the carbanion center (Verner, Cohen, *J. Am. Chem. Soc.*, 114, 375)
3. Proposed by Mikami and Takai to efficiently explain stereochemistries of alkene and nonallylic substituents in rearrangement products of elaborate allylic ethers

Mikami and Nakai's model:

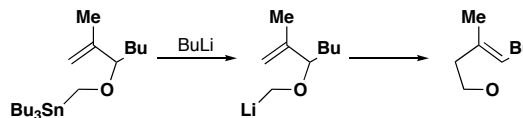


Sulfides and amines undergo hetero-Wittig shifts:

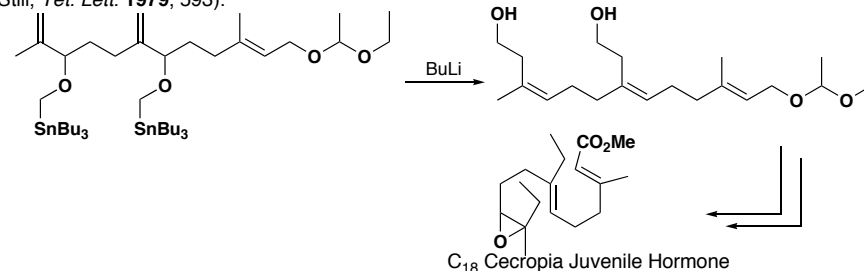


Transmetalation

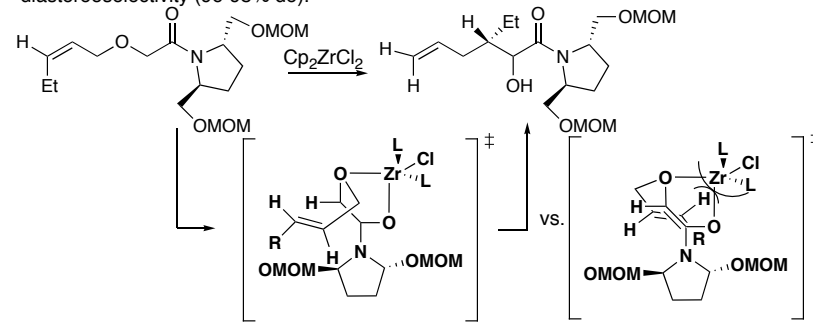
Initiation of the [2,3] Wittig rearrangement can be achieved directly by lithium insertion into a C-H bond or by transmetalation of more easily prepared compounds or if the lithiate is impossible to generate directly.



This method was first demonstrated by Still in his synthesis of C₁₈ Cecropia Juvenile Hormone (Still, *Tet. Lett.* **1979**, 593).



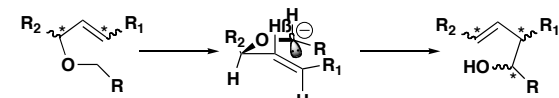
Alternatively, metals such as Zr and Hf have been used in creating organometallic complexes which adopt a geometry to undergo the [2,3] Wittig rearrangement with very high diastereoselectivity (96-98% de).



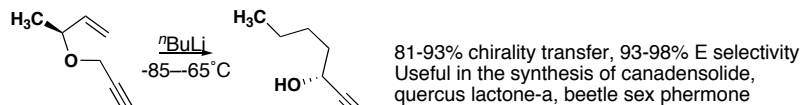
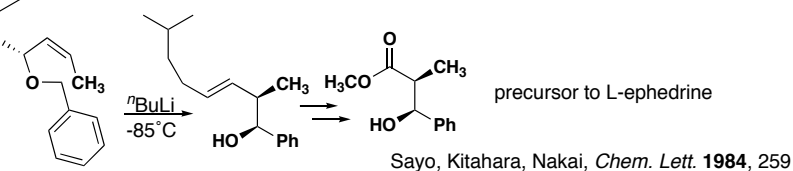
Uchikawa et al., *Tet. Lett.* **27(38)**, **1986**, 4577-80

Gallagher

Self immolative asymmetric synthesis—
Stereocontrolled formation of two chiral centers and one diastereomeric center in the product based on the chiral center and double bond geometries of the starting material.

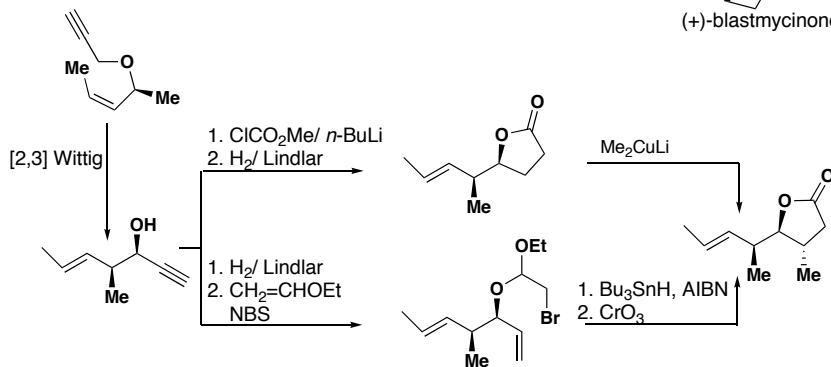
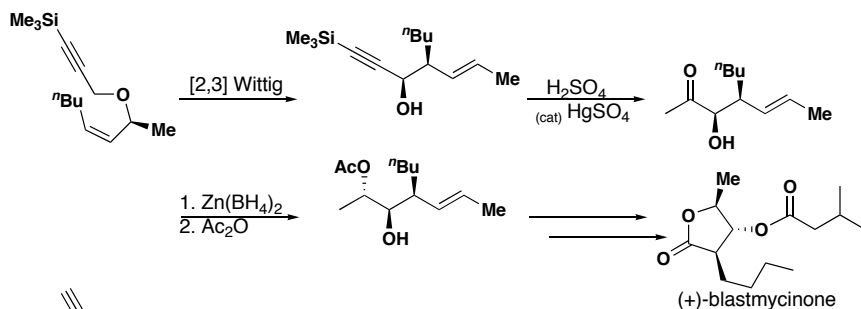


Examples—

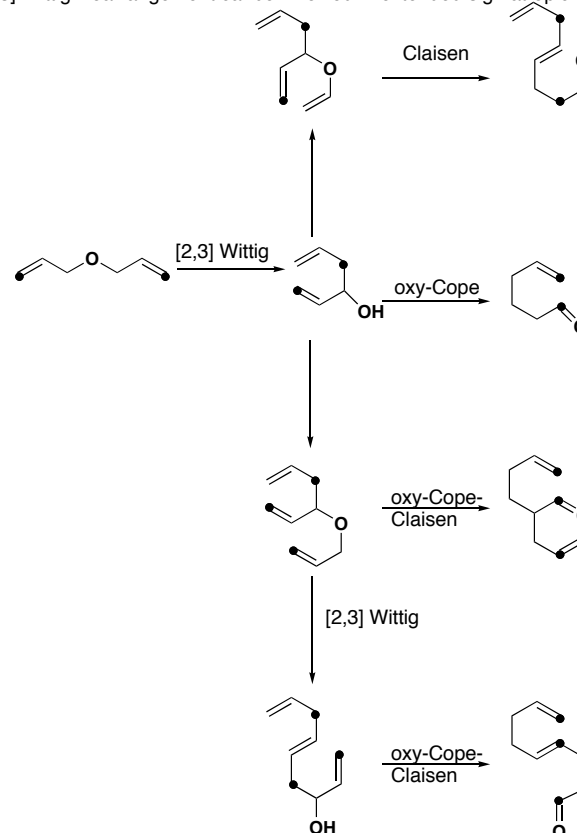


Shirai, Sayo, Nakai, *Abstracts of Papers, 48th Chemical Society of Japan Meeting, Tokyo, 1984*

The formation of two chiral centers can influence the formation of a third:



The [2,3] Wittig Rearrangement can be involved in extended sigmatropic rearrangements—



An interloper?

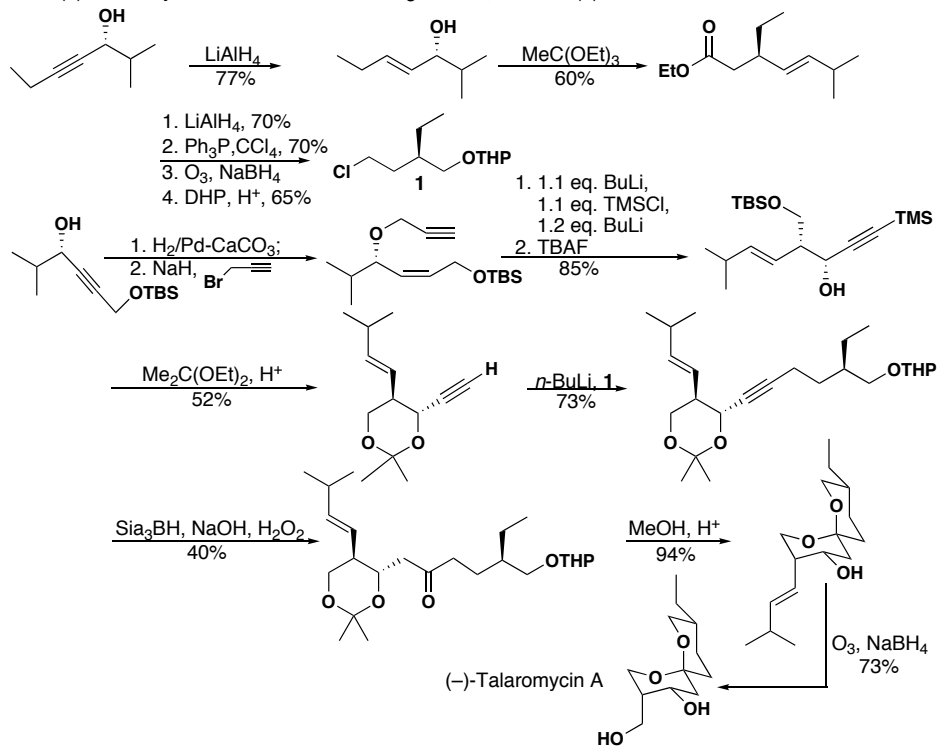
Fleming proposes that the carbanion and the ethereal oxygen are conjugated, allowing the reaction to be pericyclic. While there may be back donation of the carbanion into the allyl π^* C-O orbital, this can hardly yield full conjugation without disintegrating the ether. Instead of a concerted reaction, one would see recombination of formaldehyde and allyl anion, which calculation indicates to be the lowest energy pathway (Haefner et al., *J. Org. Chem.*, **2003**, *68*, 2310)



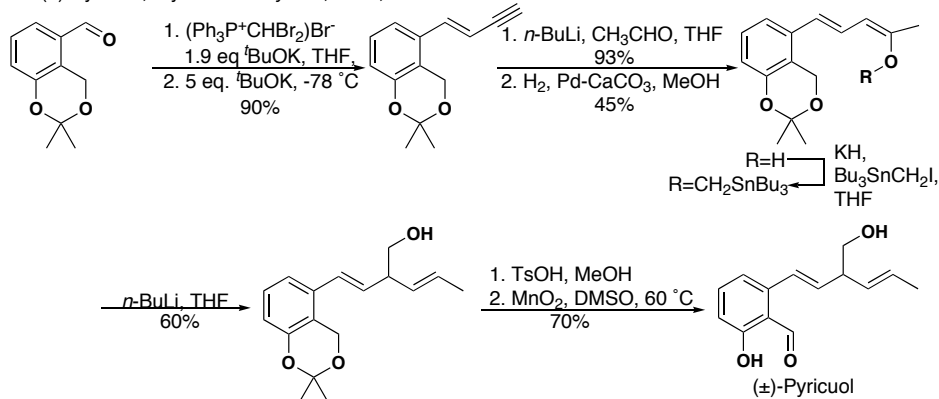
By coordinating a cation in solution, a concerted reaction is somewhat feasible (Houk et al., *J. Org. Chem.*, **1990**, *55*, 1421), however higher in energy than the fragmentation pathway. Therefore, the effect of ancillary elements, such as metallic counter ions may somehow account for the concerted nature of the reaction.

SYNTHESES

(-)-Talaromycin A, Midland et. al., *J. Org. Chem.*, **1985**, *50*(7), 1143



(±)-Pyricuol, Kiyota et. al. *Synlett*, **2003**, 219



(±)-Kainic Acid, Anderson et. al., *J. Org. Chem.*, **2003**, *68*, 6160

