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Acyclic Stereocontrol *via* Sequential and Tandem [2,3]-Wittig-Anionic Oxy-Cope Rearrangements

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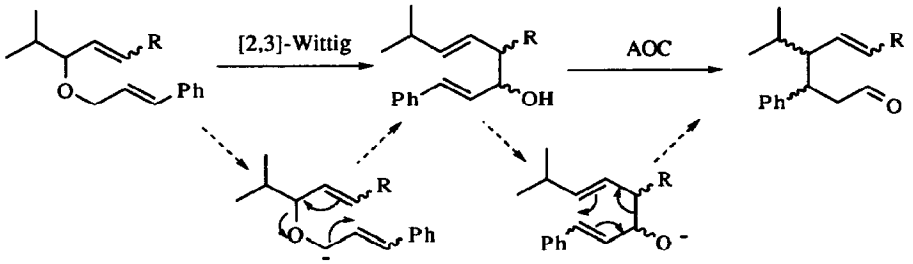
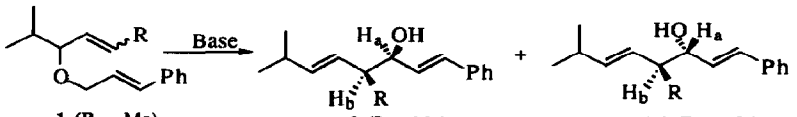
Abstract: Acyclic bis-allylic ethers undergo a stereoconvergent 'one-pot' tandem [2,3]-Wittig-anionic oxy-Cope (AOC) rearrangement to give the same δ,ε-unsaturated aldehyde, with *Esyn* stereochemistry, as that obtained by AOC rearrangement of isolated [2,3]-Wittig products.

Tandem reactions provide an opportunity for linking the synthetic power of two or more transformations in a single synthetic operation.[1] Sigmatropic rearrangements such as the [2,3]-Wittig[2] and the AOC[3,4] have been widely used to set up stereocentres by rearrangement through predictable five- and six-membered transition states. Nakai and co-workers[5] have noted the synthetic potential of *sequential* [2,3]-Wittig-AOC rearrangements for acyclic stereocontrol and asymmetric transmission. We have recently reported the first example of a *'one-pot'* tandem [2,3]-Wittig-AOC rearrangement of *(E)*-cinnamyl bis-allylic ether substrates, effected with KH in DMSO (Scheme 1).[6] We demonstrated that the tandem sequence was *stereoconvergent* and proceeded with a high level of diastereocontrol, which could be translated into the diastereoselective synthesis of substituted tetrahydropyrans. We now report our results from the tandem reactions of several bis-allylic ether substrates of different geometry and show that, in each case, the same major δ,ε–unsaturated aldehyde product with *Esyn* stereochemistry is obtained as arises from the AOC rearrangement on isolated [2,3]-Wittig products.



Scheme 1. Sequential and Tandem [2,3]-Wittig-AOC rearrangement of bis-allylic ethers

The *(E)*-cinnamyl bis-allylic ether substrates **1** (R = Me) and **2** (R = *n*-Bu) were synthesised from (*E*)-cinnamyl bromide and the corresponding allylic alcohols as described previously,[6] with good stereocontrol of the two double bonds. The [2,3]-Wittig rearrangement could be effected with a variety of bases to give *syn* and *anti* alcohols *syn*-**3**, *syn*-**4** and *anti*-**3**, *anti*-**4** respectively. Selected results are shown in Table 1.



1 (R = Me)
2 (R = *n*-Bu)

syn-**3** (R = Me)
syn-**4** (R = *n*-Bu)

anti-**3** (R = Me)
anti-**4** (R = *n*-Bu)

Table 1. [2,3]-Wittig rearrangements of bis-allylic ethers **1, 2** in THF at -78 °C

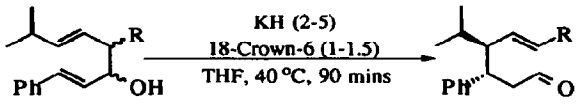
Entry	Substrate[a]	Substrate Geometric Purity *E* : *Z*	Conditions	Yield/%	Product Ratio[b] *Syn* : *Anti*
1	(*Z*,*E*)-**1**	0 : **100**	*n*-BuLi/TMEDA	50	**83** : 17
2	(*Z*,*E*)-**2**	0 : **100**	*n*-BuLi (2 eq.)	63	**86** : 14
3	(*E*,*E*)-**1**	**100** : 0	*t*-BuLi	46	38 : **62**
4	(*E*,*E*)-**1**	**100** : 0	*n*-BuLi/NaO*t*-Bu	84	37 : **63**
5	(*E*,*E*)-**1**	**100** : 0	*n*-BuLi (2 eq.)	79	34 : **66**
6	(*E*,*E*)-**2**	**100** : 0	*n*-BuLi (2 eq.)	76	26 : **74**

[a] First letter in parenthesis refers to variable olefin geometry. [b] Measured from ratio of H_a signals in ^{1}H NMR

The [2,3]-Wittig rearrangements all resulted in 100% *(E)*-olefin selectivity and exclusive formation of the regioisomer from deprotonation at the unsubstituted carbon atom.[2] The results also showed that *(Z)*- and *(E)*-olefins rearranged to give opposite diastereoisomers, as predicted by consideration of Nakai's folded envelope transition states in which the allyl anion prefers to adopt an equatorial orientation.[2] The sense of diastereoselectivity was established by comparison with the chemical shifts and coupling constants obtained by Midland for similar compounds.[7] Rearrangement of (Z)-olefins was found to be more selective than rearrangement of *(E)*-olefins, as observed previously. The highest selectivity for rearrangement of an (*E*)-substrate was 74:26, from rearrangement of the butyl substituted bis-allylic ether *(E,E)*-**2** (Entry 6), whilst a ratio of up to 86:14 in favour of the *syn* diastereoisomer could be obtained from rearrangement of a *(Z)*-substrate, *(Z,E)*-**1** (Entry 2). The selectivity was not affected by carrying out the rearrangement at lower temperatures down to -125 °C.

Use of one equivalent of *n*-BuLi resulted in isolation of 50% or less of the [2,3]-Wittig product, even in the presence of activating agents such as TMEDA[8] (Entry 1) due to the reaction not going to completion. Use of a stronger base such as *t*-BuLi (Entry 3) also failed to improve the yield. The Schlosser base combination of *n*-BuLi and NaO*t*-Bu, recently used by Lipshutz[9] gave rise to one high yielding reaction (Entry 4). However reproducibly high yields were finally obtained by addition of two equivalents of *n*-BuLi at the start of the reaction (Entries 2, 5, and 6).

Single diastereoisomers of the [2,3]-Wittig products **3** and **4** were obtained by preparative HPLC separation of the [2,3]-Wittig reaction mixtures and were subjected to AOC rearrangement using standard conditions[10] (KH, 18-crown-6 in THF) to give the δ,ε-unsaturated aldehydes **5** and **6** (Table 2).



3; R = Me
4; R = *n*-Bu

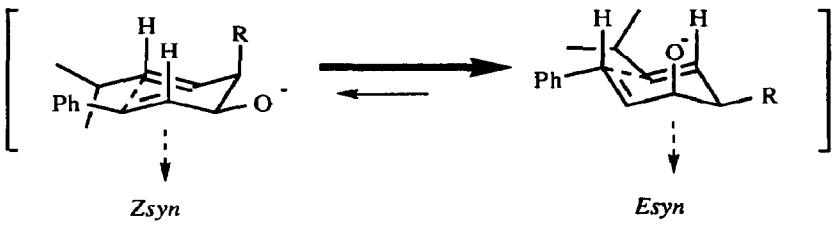
5; R = Me
6; R = *n*-Bu

Table 2. Anionic oxy-Cope rearrangements of alcohols **3, 4**

Entry	Substrate	Substrate Purity *Syn* : *Anti*	Yield %	Product Ratio[a] *Esyn:Zsyn:Eanti*	*%E*	*%Syn*
1	*anti*-**3**	39 : **61**	62	**61** : 18 : 21	82	79
2	*anti*-**3**	0 : **100**	41	**58** : 27 : 15	73	85
3	*anti*-**4**	0 : **100**	55	**64** : 24 : 12	76	88
4	*syn*-**3**	**100** : 0	55	**77** : 8 : 15	92	85
5	*syn*-**4**	**96** : 4	58	**82** : 9 : 9	91	91

[a] Measured from ratio of olefinic protons in ^{1}H NMR

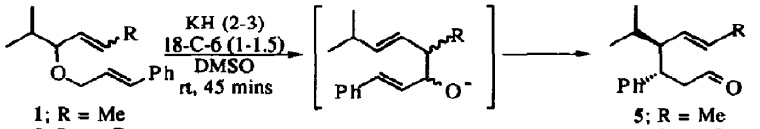
In each reaction, AOC rearrangement gave rise to three isomeric aldehydes. The same major isomer was formed regardless of substrate stereochemistry, demonstrating that the AOC rearrangement of these substrates is a stereoconvergent reaction. Inspection of the 400 MHz ^{1}H NMR spectrum showed that this isomer had *(E)*-olefin geometry (J = 15 Hz) and conversion to the iodotetrahydropyran by a halocyclisation reaction showed it to have *syn* relative configuration.[6] Two minor isomers were also formed, with *(E)*- and *(Z)*-olefin geometry. Hydrogenation of a mixture of isomers demonstrated that the minor *(Z)* product also had *syn* relative configuration.[6] These two *syn* diastereoisomers must be formed through chair transition states, as previously described by Mikami and Nakai.[5] The minor *(E)* aldehyde with *anti* relative stereochemistry is likely to be formed through a boat transition state. Rearrangement of *syn* stereochemistry substrates (Entries 4 and 5) was more selective than rearrangement of *anti* substrates (Entries 1,2 and 3) probably due to a highly favoured chair transition state with all substituents equatorial. The formation of the same δ,ε-unsaturated aldehyde product with *Esyn* stereochemistry from rearrangement of *anti* substrates demonstrates that AOC rearrangement through a transition state in which the oxy-anion is axial is possible in acyclic systems, when the alternate transition state is destablised by another pseudo-diaxial interaction (Figure 1). This compares with Paquette's recent results for the AOC rearrangement of *simple* acyclic molecules in which he found a weak preference for the oxy-anion to be equatorial.[10] Entry 1 indicates that separation of diastereoisomers prior to rearrangement is not necessary for moderate levels of selectivity.



Zsyn *Esyn*

Figure 1

For the 'one-pot' tandem [2,3]-Wittig-AOC reaction we required a base, or more specifically a counter-ion, which would effect both transformations. Lithium and sodium bases were not useful, even in the presence of powerful sequestering agents such as 12-crown-4 or the [2.1.1]-cryptand Kryptofix®211.[11] The transformation was finally achieved by treatment of the bis-allylic ether substrates with KH/18-crown-6 in DMSO.[12] The results are shown in Table 3.



1; R = Me
2: R = *n*-Bu

5; R = Me
6; R = *n*-Bu

Table 3. Tandem rearrangement of bis-allylic ethers **1, 2**

Entry	Substrate	Substrate Purity *E* : *Z*	Yield/ %	Product Ratio[a] *Esyn* :*Zsyn*:*Eanti*	%*E*	%*Syn*
1	(*E*,*E*)-**1**	**100** : 0	52	**71** : 18 : 11	82	89
2	(*E*,*E*)-**2**	**100** : 0	55	**78** : 17 : 5	83	95
3	(*Z*,*E*)-**1**	3 : **97**	57[b]	**73** : 17 : 10	83	90
4	(*Z*,*E*)-**2**	0 : **100**	44	**74** : 19 : 7	81	93

[a] Measured from ratio of GC peaks [b] Yield of alcohol product, formed by reduction with sodium borohydride

Reaction was found to be very rapid, occurring in 45 minutes at room temperature. Like the AOC rearrangement on *isolated* [2,3]-Wittig substrates, the tandem reaction gave the same major isomer with *Esyn* stereochemistry regardless of substrate double bond geometry. Surprisingly, from the results for the separate rearrangements, the highest selectivity was obtained from rearrangement of an (*E*)-substrate (Entry 2) which gave 83% *E* selectivity and 95% *syn* selectivity. In all reactions, about 15% of the yield could be attributed to products from a competing [1,2]-Wittig-AOC transformation; it was not possible to separate these isomers by flash chromatography.

Thus we have demonstrated the viability of both the AOC rearrangement and the tandem [2,3]-Wittig-AOC rearrangement as methods for acyclic stereocontrol. Efforts are underway to improve both the scope and selectivity of the these transformations.

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