Pergamon

Tetrahedron Letters, Vol. 38, No. 36, pp. 6445-6448, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01473-1

Stereoselective [2,3]-Wittig and Tandem [2,3]-Wittig-Anionic Oxy-Cope Rearrangements of Bis-allylic Ethers : Effect of Substituents

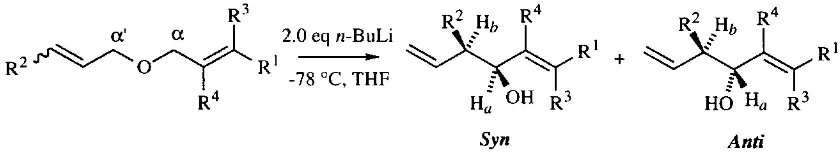
Nicholas Greeves* and Wai-Man Lee

Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, Crown St, Liverpool, L69 7ZD, U.K.

Abstract: Acyclic bis-allylic ethers undergo, *syn* or *anti* stereoselective [2,3]-Wittig rearrangement to give homoallylic alcohols depending on the substituents, and *E*-selective tandem [2,3]-Wittig-anionic oxy-Cope rearrangement to give δ,ε-unsaturated aldehydes. © 1997 Elsevier Science Ltd.

Sigmatropic rearrangements such as [2,3]-Wittig[1-2], [3,3]-anionic oxy-Cope (AOC)[3-5] and Claisen[6] which permit the generation of stereocentres by concerted processes through predictable five- and six-membered transition states play an increasingly important role in modern organic synthesis. Tandem reactions, in which two or more sigmatropic rearrangements are performed in a single operation, can provide an opportunity for extending their synthetic utility.[7-9] We have previously reported the first example of a 'one-pot' tandem [2,3]-Wittig-AOC rearrangement of *E*-cinnamyl bis-allylic ether giving δ,ε-unsaturated aldehydes and the stereochemistry was determined by conversion to substituted iodotetrahydropyrans.[10] The tandem sequence was demonstrated to be stereoconvergent so that the diastereoselectivity of the [2,3]-Wittig rearrangement leading to homoallylic alcohols does not affect the stereochemistry of the final δ,ε-unsaturated aldehydes which converge to the same adduct.[11]

The interpretation of the stereochemical outcome of the tandem rearrangement was complicated by the presence of two stereocentres and an alkene in the product which gave rise to at least four products. We now report the effect of steric bulk of alkyl groups R^1 and R^2 on the diastereoselectivity of homoallylic alcohols after simple [2,3]-Wittig rearrangement and tandem reaction in systems that lack the second stereocentre and hence allow study of the factors governing alkene geometry in the tandem product. Various potential anion stabilising groups (R_3Si, R_3Sn, PhS, CF_3) have been introduced in the place of the phenyl group used in the original work to control the regioselectivity of deprotonation (α vs α') in an attempt to broaden the scope of the tandem process and to assess their compatibility with the tandem conditions.



Scheme 1. Stereoselective [2,3]-Wittig rearrangement of bis-allylic ethers

The required bis-allylic ethers were prepared in excellent yield by alkylation of the corresponding allylic alcohols with allylic bromides such as cinnamyl or crotyl bromide in the presence of sodium hydride and catalytic amount of tetrabutylammonium iodide in THF. Cinnamyl bromide gave a single geometric isomer of the bis-allylic ethers but crotyl bromide gave a mixture of *E*- and *Z*-isomers. Regioselective deprotonation at the α position with strong base gave rise to both diastereoisomers of homoallylic alcohols in excellent yield after [2,3]-Wittig rearrangement (Scheme 1).

Table 1 summarises the results of [2,3]-Wittig rearrangements and it shows that altering the steric bulk of alkyl groups R^1 and R^2 profoundly affects the diastereoselectivity. Either *syn* or *anti* products were produced preferentially depending on the demands of the substituents. The diastereoisomers were distinguished by the analysis of chemical shifts and coupling constants of methine proton H_a located next to the hydroxyl group by ^1H NMR analysis.[12] The stereoselectivity is generally consistent with Nakai's folded envelope transition state analysis in which the allylic anions prefer to adopt an equatorial orientation and so *E*-alkenes form predominantly *anti* products.[13] However, the opposite sense of distereoselectivity was observed when bulky substituents, such as a *t*-Bu group, or a bulky silyl group in one allylic fragment were introduced (entries 6, 7, 12, 13, 14 and 15). The unusual diastereoselectivity may be explained by consideration of the transition states leading to the *syn* and *anti* products (Figure 1). If the gauche repulsion between the allylic fragment G and the alkyl substituent is sufficiently large, it may prevail forcing the allylic fragment G to adopt an axial orientation in spite of the pseudodiaxial interaction.

As we had hoped, phenyl, phenylthio, silyl and stannyl functionalities all exhibited allylic anion stabilising capability resulting in regioselective deprotonation and regioselective [2,3]-Wittig rearrangement which is required for the tandem sequence. Unfortunately the trifluoromethyl group was not powerful enough to direct the deprotonation and a complex mixture resulted(entry 16).

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

Entry	R^1	R^2	R^3	R^4	Substrate geometry[a] *E* : *Z*	Time / h	Yield /%	Product ratio[b] *syn* : *anti*
1	Ph	Me	H	H	98 : 2	5	85	23 : **77**
2	Ph	*n*-Pr	H	H	100 : 0	5	86	13 : **87**
3	Ph	*n*-Pr	H	H	0 : 100	5	94	**80** : 20
4	Ph	*n*-Bu	H	H	100 : 0	5	84	20 : **80**
5	Ph	*i*-Pr	H	H	100 : 0	5	91	22 : **78**
6	Ph	*t*-Bu	H	H	100 : 0	4	77	**88** : 12
7	Ph	*t*-Bu	H	Me	100 : 0	6	80	**93** : 7
8	SPh[d] (*E* : *Z* = 2.7:1)	Me	H	H	67 : 33[e]	6	70	*E*=38:**62** *Z*=43:**57**
9[c]	Bu_3Sn	Me	H	H	78 : 22	6	81	49 : **51**
10[c]	H	Me	H	Bu_3Sn	80 : 20	6	70	22 : **78**
11	$SiMe_2$*t*-Bu	*i*-Pr	H	H	100 : 0	1.5	87	22 : **78**
12	$SiMe_2$*t*-Bu	Me	H	H	71 : 29	1.5	84	**68** : 32
13	$SiMe_2Ph$	*t*-Bu	H	H	100 : 0	1.5	84	**83** : 17
14	$SiMe_2Ph$	Me	H	H	71 : 29	1.5	88	**62** : 38
15	$SiMe_3$	Me	H	H	78 : 22	1.5	91	**60** : 40
16	CF_3	Me	Me	H	81 : 19	5	61	complex mixture

[a] *E*:*Z* ratio measured by GC; [b] Ratio measured by ^1H NMR of H_a ; [c] LDA used as base; [d] ratio of SPh fragment measured by ^1H NMR; [e] ratio of crotyl fragment measured by ^1H NMR.

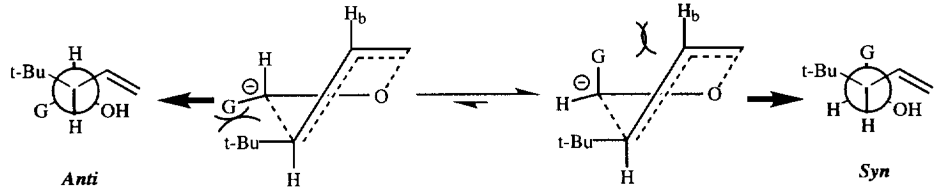
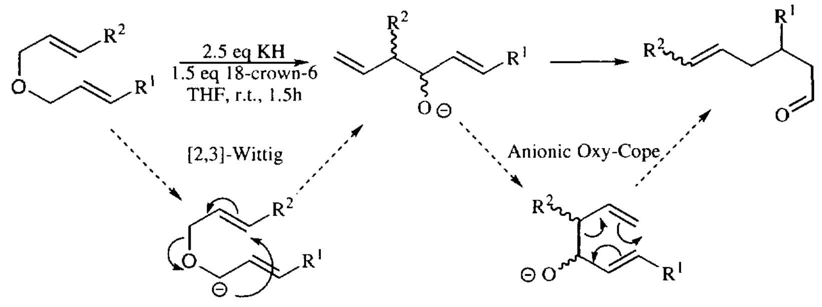


Figure 1. Transition states for [2,3]-Wittig rearrangement

The tandem [2,3]-Wittig-AOC rearrangement (Scheme 2), accomplished by treatment of the bis-allylic ethers with potassium hydride and 18-crown-6 in either THF or DMSO, was complete after 1.5 hours to give δ,ε-unsaturated aldehydes (Table 2). Despite a slightly faster reaction rate - the reaction usually being complete within an hour in DMSO[14] - an improvement in isolated yield with no loss of *E/Z* selectivity in the resulting aldehyde was found consistently when DMSO was replaced by THF (entries 1, 11, and 13). The potassium enolate of the aldehyde generated after AOC rearrangement was very sensitive to the quench used. Both acidic (NH_4Cl, HCl and H_2SO_4) and basic ($NaHCO_3$) quenches gave lower yields due to the formation of an aldol dimer. Quenching with phosphate buffer (pH 7.0, KH_2PO_4 and NaOH) gave dramatically improved yields without this undesired byproduct.[15]

The outcome is in accordance with a six-membered chair transition state in which the alkyl substituents R^2 favour an equatorial orientation leading to the *E*-aldehyde but there may still be a weak preference for the oxyanion to adopt an equatorial orientation depending on structural features (Figure 2).[16] A mixture of *E* and *Z* isomers, favouring the *E* configuration, was observed if relatively non bulky substituents R^2 were used (entries 1-7 and 11-15) and lowering the reaction temperature to 0 °C improved the alkene ratio slightly (entries 3 and 5). Silyl and stannyl functionalised substrates subjected to the same conditions only gave moderate yields (entries 11-15) presumably due to the instability of the β-silyl and β-stannyl aldehyde enolates to nucleophilic attack by alkoxides. The isolation of the corresponding silanols was additional evidence for this cleavage.



Scheme 2.

Table 2. Tandem [2,3]-Wittig-AOC rearrangement of bis-allylic ethers

Entry	R^1	R^2	Substrate geometry *E* : *Z*	Solvent	Yield / %	Aldehyde geometry *E* : *Z*
1	Ph	Me	98 : 2	DMSO	55	75 : 25
2	Ph	Me	98 : 2	THF	76	75 : 25
3	Ph	Me	98 : 2	THF	76	85 : 15[a]
4	Ph	*n*-Pr	100 : 0	THF	79	84 : 16
5	Ph	*n*-Pr	100 : 0	THF	79	86 : 14[a]
6	Ph	*n*-Pr	0 : 100	THF	67	79 : 21
7	Ph	*n*-Bu	100 : 0	THF	80	79 : 21
8	Ph	*i*-Pr	100 : 0	THF	67	**100** : 0
9	Ph	*t*-Bu	100 : 0	THF	73	**100** : 0
10	SPh	Me	67 : 33	THF	0[b]	-
11	$SiMe_3$	Me	78 : 22	DMSO	32	62 : 38
12	$SiMe_3$	Me	78 : 22	THF	50	62 : 38
13	$SiMe_2$*t*-Bu	Me	71 : 29	DMSO	24	62 : 38
14	$SiMe_2$*t*-Bu	Me	71 : 29	THF	59	62 : 38
15	$SnBu_3$	Me	78 : 22	THF	48	67 : 33

[a] Reaction initiated at 0 °C and then warmed to room temperature; [b] Decomposed with generation of thiophenol.

Bulky R^2 substituents gave exclusively *E*-aldehydes (entries 8 and 9) characterized by *trans* coupling of olefinic protons (J = 15.4 Hz). The results suggested that only transition state T_E existed during the rearrangement. Transition state T_Z is presumably too unstable due to the pseudodiaxial interaction between either *i*-propyl or *t*-butyl group and the protons shown. Overall the results from temperature and steric effects are consistent with the reaction proceeding *via* both T_Z and T_E with the extent of dominance of T_E being determined by the steric bulk of R^2.

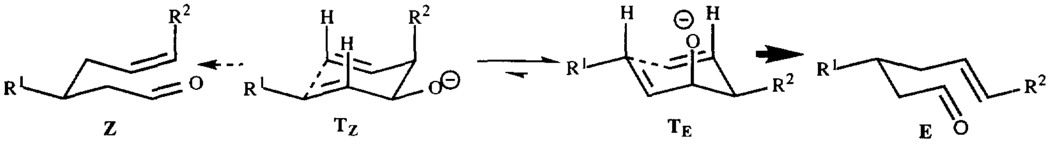


Figure 2. Transition states for AOC rearrangement

In conclusion, we have demonstrated the effect of steric bulk of alkyl groups R^1 and R^2 on the diastereoselectivity of [2,3]-Wittig rearrangement and geometric control in the tandem reaction and that very high levels of selectivity are achievable in certain systems. The resulting δ,ε-unsaturated aldehydes can either be reduced to the corresponding alcohols or oxidised to the carboxylic acids. Both of these are substrates for stereoselective, electrophile initiated cyclisation producing tetrahydropyrans and δ-lactones respectively. The success of these processes is reported in the following letters.[17]

Typical experimental procedure for tandem reaction.

Dry THF (50 ml) was transferred under argon atmosphere to potassium hydride (previously washed and dried *in vacuo*) (14 mmol) in a dry Schlenk flask. 18-crown-6 (8.3 mmol) in dry THF (10 ml) was added and the solution was stirred for 15 minutes. Bis-allylic ether (5.5 mmol) was added in one portion in small volume of dry THF. The mixture was stirred for 1.5 h before the dark brown solution was poured onto a mixture of ice and phosphate buffer (pH 7.0) in a separating funnel. The layers were separated and the aqueous layer was extracted with diethyl ether (3x). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography, eluting with diethyl ether-light petroleum (bp 40-60 °C) to yield a yellow oil (4.4 mmol, 80%).

Acknowledgements: We would like to thank ORS for the partial financial support.

References and Notes:

1. Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, 86, 885-902, Nakai, T.; Mikami, K. *Org. React.*,**1994**, *46*, 105-209.
2. Marshall, J. A. *Comprehensive Organic Synthesis*; B. M. Trost, Ed.; Pergamon: 1991; Vol. **3**. pp975-1014
3. Wilson, S. R. *Organic Reactions*; Paquette, L. A. Ed.; John Wiley & Sons Inc.: New York, **1993**; Vol. 43; pp 93-251.
4. Lee, E.; Lee, Y. R.; Moon, B.; Kwon, O.; Shim, M. S.; Yun, J. S. *J. Org. Chem.*, **1994**, 59, 1444-1456.
5. Paquette, L. A.; Liang, S.; Wang, H-L. *J. Org. Chem.*, **1996**, 61, 3268-3279.
6. Hill, R. K. *Comprehensive Organic Synthesis*; B. M. Trost, Ed.; Pergamon: 1991; Vol. **5**; pp785-826.
7. Ho, T-L. *Tandem Organic Reactions*; John Wiley & Sons, Inc.: New York, **1992**.
8. Bunce, R. A. *Tetrahedron*, **1995**, 51, 13103-13159.
9. Mitchell, T. N.; Giesselmann, F. *Synlett.*, **1996**, 475-476.
10. Greeves, N.; Vines, K. J. *J. Chem. Soc., Chem Commun.*, **1994**, 1469-1470.
11. Greeves, N.; Vines, K. J. *Tetrahedron Lett.*, **1994**, 35, 7077-7080.
12. H_a in the *syn* isomers is always 0.1-0.3 ppm downfield of the same proton in the *anti* isomer for all alcohols and the vicinal coupling constants in the *anti* isomer, between H_a and H_b, have been found to be 1.0-1.5 Hz higher than corresponding coupling in the *syn* isomers. Similar results have been observed previously by Tsai, D. S. J.; Midland, M. M. *J. Org. Chem.*, **1984**, 49, 1842-1843.
13. Nakai, T.; Mikami, K. J. *Synthesis*, **1991**, 594-604.
14. Gajewski, J. J.; Gee, K. R. *J. Am. Chem. Soc.*, **1991**, 113, 967-971.
15. Under acidic or basic quenching conditions the major product was the dimer of expected aldehyde after aldol reaction and elimination of water as confirmed by mass spectrometry ($[2M-H_2O]^+$) and ^1H NMR analysis. An additional olefinic proton signal appeared as triplet doublet at δ 6.3 (td, J = 6.6 and 1.6 Hz) and the aldehyde proton was shifted from the usual δ 9.7 (t, J = 2.2 Hz) to δ 9.2 (d, J = 1.1 Hz) and displayed reduced multiplicity.
16. Paquette, L. A. *Angew. Chem. Int. Ed. Engl.*, **1990**, 29, 609-626.
17. Following papers in this issue, Greeves, N.; Lee, W. M. *Tetrahedron Lett.*, **1997**, 38, 6449 and Greeves, N.; Lee, W. M., Barkley, J. V. *Tetrahedron Lett.*, **1997**, 38, 6453.

(*Received in UK* 5 *June* 1997; *revised* 16 *July* 1997; *accepted* 18 *July* 1997)