Pergamon

Tetrahedron Letters 42 (2001) 1317–1320

TETRAHEDRON LETTERS

Strict base dependence of chirality transfer on [2,3]-Wittig rearrangement of 1,1,2-trifluoroallylic ether

Toshiyuki Itoh* and Kazutoshi Kudo

Department of Chemistry, Faculty of Education, Okayama University, Okayama 700-8530, Japan

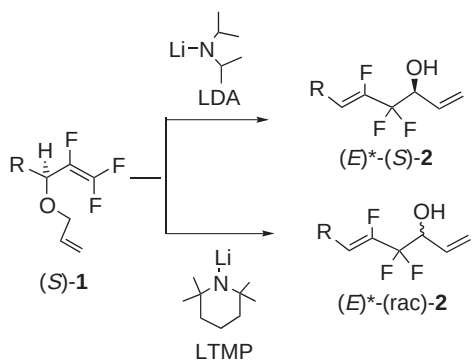
Received 10 October 2000; revised 17 November 2000; accepted 1 December 2000

Abstract—Investigation of [2,3]-Wittig rearrangement of optically active 1,1,2-trifluoroallylic ether revealed that chirality transfer of the starting compound strictly depended on the base employed, while stereoselectivity of the newly formed olefinic part was controlled with perfect (*E*)-selectivity. Because the reaction was inhibited by addition of TEMPO; these results suggested [2,3]-Wittig reaction proceeded via a radical pathway mechanism.

The synthesis of partly *gem*-difluorinated compounds remains a significant challenge to synthetic organic chemists.[1] As part of a program aimed at synthesizing partly difluorinated analogues of insect pheromone,[2] we accomplished a highly stereoselective synthesis of 4,4,5-trifluoroalka-1,5-dien-3-ols through [2,3]-Wittig rearrangement of 1,1,2-trifluoroallylic ethers.[3] While performing further study, we found the very interesting fact that the optical purity of the resulting product **2** strictly depended on the base employed when optically active starting allylic ether **1** was subjected to the reaction (Scheme 1).

(*E*)*-(*S*)-8-Phenyl-4,4,5-trifluorooct-1,5-diene-3-ol (**2**)[4] was obtained when (*S*)-5-phenyl-1,1,2-trifluoro-1-pent-3-yl allyl ether (**1**)[5] was subjected to the [2,3]-Wittig rearrangement; enantiomeric excess of product **2** was slightly reduced (82% ee) from that of starting allylic ether (**1**) (95% ee) when the reaction was carried out in the presence of lithium diisopropylamide (LDA) as base. The rearrangement product **2** was obtained as a racemic form (ca. 5% ee) when lithium tetramethylpiperidide (LTMP) was employed as base using the same 90% ee of allylic ether **1**. However, the stereoselectivity of both reactions for the newly formed olefinic part was controlled with perfect (*E*)-selectivity. These dramatic differences in the two reactions prompted us to investigate details of the rearrangement using an optically active allylic ether as the starting compound.

Allylic ether (*S*)-**1** was treated with LDA at −100°C in tetrahydrofurane (THF) for 6 h, and the resulting mixture was allowed to warm up to rt for 14 h with stirring. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution and silica gel flash column chromatography gave the rearrangement product **2** with 82% ee in 58% yield (Table 1, entry 1). The absolute configuration of the product was determined to be (*S*)-form by the modified Mosher method proposed by Kusumi and colleagues.[6] Change of base to LTMP from LDA caused a drastic reduction in the optical purity of product **2** in both solvent systems of ether (Et_2O) and THF (entries 3 and 6). Interestingly, butylated compound **3a** was obtained as the sole product when the reaction was carried out using *n*-BuLi as base in the ether solution (entry 7), while the reaction in THF did not afford butylated compound **3a**



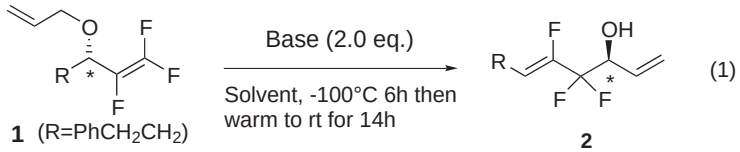
Scheme 1.

Keywords: [2,3]-Wittig rearrangement; optically active 1,1,2-trifluoroallylic ether; radical pathway.

* Corresponding author. Fax: +81-96-251-7639; e-mail: titoh@cc.okayama-u.ac.jp

0040-4039/01/$ - see front matter
PII: S0040-4039(00)02236-X

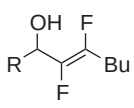
Table 1. Results of [2,3]-Wittig rearrangement of allylic ether **1**

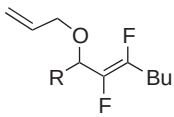


1 (R=PhCH$_2$CH$_2$) **2**

Entry	% ee of **1** (config.)	Base	Solvent	Additive[a]	Yield of **2**[b] (%)	% ee of **2**[c] (config.)	(*E*)*-**2**:(*Z*)*-**2**[d]
1	95 (*S*)	LDA	THF	None	58	82 (*S*)	>99:<1
2	87 (*R*)	LDA	THF	None	60	75 (*R*)	>99:<1
3	90 (*S*)	LTMP	THF	None	64	5 (*S*)	>99:<1
4	77 (*R*)	LTMP	THF	None	62	5 (*R*)	>99:<1
5	99 (*S*)	LDA	Et_2O	None	50	70 (*S*)	>99:<1
6	99 (*S*)	LTMP	Et_2O	None	60	8 (*S*)	>99:<1
7	99 (*S*)	*n*-BuLi	Et_2O	None	[e]	[e]	[e]
8	90 (*R*)	LDA	THF	TEMPO	0	[f]	–
9	90 (*R*)	LDA	THF	TEMPO[g]	0	[f]	–
10	90 (*R*)	LDA	THF	TMEDA	70	75 (*R*)	>99:<1
11	99 (*S*)	LDA	THF	HMPA	66	73 (*S*)	>99:<1
12	90 (*R*)	LTMP	THF	TEMPO	0	[f]	>99:<1
13	90 (*R*)	LTMP	THF	TEMPO[g]	41	31 (*R*)	>99:<1
14	90 (*R*)	LTMP	THF	TMEDA	64	8 (*R*)	>99:<1
15	90 (*R*)	LTMP	THF	HMPA	81	2 (*R*)	>99:<1

[a] Added 1.0 equiv. towards the substrate.
[b] Isolated yield.
[c] Determined by HPLC analysis using chiral column (Chiralcel OD, hexane:*i*-PrOH = 19:1).
[d] Determined by capillary GC analysis (MS-25M). Because the fluorine atom is superior to the carbon atom, this nomenclature does not follow the IUPAC rule. We adapted this nomenclature to discuss the stereochemistry of [2,3]-Wittig rearrangements. (*E*)* and (*Z*)* correspond to (*Z*) and (*E*), respectively.
[e] Compound **3a** (racemic) was obtained in 98% yield instead of the desired rearrangement product with perfect (*E*)-selectivity when the reaction was quenched by aq. NH_4Cl. On the other hand, allylic ether **3b** was obtained in 95% yield when the reaction was quenched by methanol at 0°C.
[f] The starting material **1** was recovered in more than 90% yield without loss of the optical purity.
[g] Added 0.1 equiv. of TEMPO.

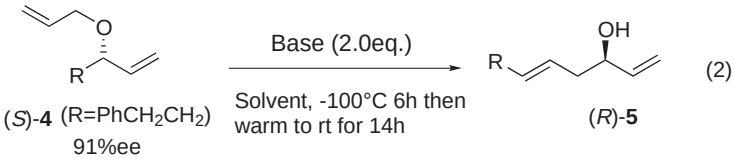

3a


3b

but only the polymerized compounds. The stereochemistry of the olefinic part of product **3a** was controlled with perfect (*E*)-selectivity, though **3a** was obtained as a racemic form (entry 7). The present [2,3]-Wittig rearrangement reaction was inhibited by addition of 1 equiv. of 2,2,6,6-tetramethyl-1-piperidine-1-oxy free radical (TEMPO), and the starting material (*R*)-**1** was recovered in more than 90% yield without any loss of optical purity (entries 8 and 12). Even more interesting was the finding that the reaction was completely inhibited by addition of only 10 mol% of TEMPO towards the substrate when LDA was used (entry 9), while being only partly inhibited by the same amount of TEMPO when the reaction was performed using LTMP as a base (entry 13).[7] We added tetramethylethylendiamine (TMEDA) or hexamethylphosphoramide (HMPA) for the purpose of improving reactivity of the anion species which formed at the initial step of the reaction, but neither the optical purity nor the chemical yield of the product was influenced by this (entries 10, 11, 14 and 15).

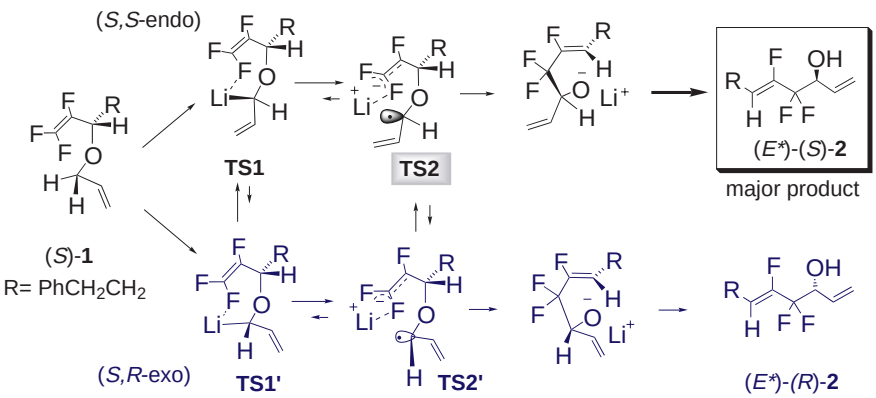
[2,3]-Wittig reaction of (*S*)-5-phenyl-1-penten-3-yl allyl ether (**4**) proceeded in a different fashion from that of the corresponding fluorinated ether (see Table 2); (*R*)-8-phenylocta-1,5-diene-3-ol (**5**)[5] was obtained in all reactions, while the optical purity was maintained at a level of more than 80% of the starting allylic ether (*S*)-**4**. Addition of 1.0 equiv. of TEMPO to the reaction mixture again completely inhibited the reaction and more than 94% of starting compound (*S*)-**4** was recovered with the original optical purity retained (entries 8 and 9). Like the reaction of fluorinated allylic ether (*S*)-**1**, 10 mol% of TEMPO caused only partial inhibition of the LTMP-mediated rearrangement reaction of (*S*)-**4** (entry 10). *A radical pathway mechanism for the [2,3]-Wittig rearrangement was proposed by Murphy and co-workers.*[8,9] *Our results strongly supported their radical pathway mechanism*, because addition of 1.0 equiv. of TEMPO completely inhibited the reaction, though the details of the reaction mechanism seemed to be different from their original hypothesis.[8] From our results, we postulated the reaction mechanism of the

Table 2. Results of [2,3]-Wittig rearrangements of allylic ether **4**



Entry	Base	Solvent	Additive[a]	Yield of **5** (%)[b]	%ee of **5**[c]	(*E*)-**5**:(*Z*)-**5**[d]
1	*n*-BuLi	THF	None	91	78	>99:<1
2	*n*-BuLi[e]	THF	None	93	77	>99:<1
3	LDA	THF	None	41	79	>99:<1
4	LTMP	THF	None	85	82	>99:<1
5	*n*-BuLi	Et_2O	None	0[f]	–	–
6	*n*-BuLi[e]	Et_2O	None	0[f]	–	–
7	LTMP	Et_2O	None	91	88	>99:<1
8	*n*-BuLi	THF	TEMPO	0[f]	–	–
9	LTMP	THF	TEMPO	0[f]	–	–
10	LTMP	THF	TEMPO[g]	67	83	>99:<1

[a] Added 1.0 equiv. towards the substrate.
[b] Isolated yield.
[c] Determined by HPLC (Chiralcel OD, hexane:*i*-PrOH = 19:1).
[d] Determined by capillary GC analysis (MS-25M).
[e] Added 1.2 equiv. towards the substrate.
[f] Starting alyllic ether **4** was recovered in more than 50% yield without loss of the original optical purity.
[g] Added 0.1 equiv. of TEMPO.



Scheme 2.

present [2,3]-Wittig rearrangement to be as illustrated in Scheme 2.

We assume that the key transition state of the rearrangement might be a radical species TS2; once TS2 was generated from TS1,[7] this triggered the reaction pathway to complete the rearrangement reaction and afforded product (*E*)*-(*S*)-**2**. Because TEMPO can trap radical species such as TS2, the reaction was inhibited by the addition of TEMPO. The differences between LDA mediated reaction and LTMP mediated reaction may reflect the differences in the equilibrium state of TS1[7] and TS2. Since LTMP is a higher sterically bulky base than LDA, a larger amount of TS2 was formed for LTMP mediated reaction than for LDA; thus 10 mol% of TEMPO completely inhibited the LDA mediated reaction (entry 9 in Table 1), while LTMP mediated reaction was only partly inhibited by this amount (entry 13 in Table 1). Yamazaki et al. suggested that the Li–F bond has an important role in determining the stereoselectivity in the 1,4-addition of an enolate with partly fluorinated Michael acceptor.[10] In our reaction, chelation of a lithium atom with fluorine atoms[11] on the olefinic part of (*S*)-**1** may contribute to the stabilization of TS2.

In conclusion, we established that a radical process might be involved in the [2,3]-Wittig reaction and therefore the stereochemical outcome would be influenced by the base employed. Further investigation on the full details of the reaction mechanism with the aid of computational chemistry is now in progress.

Acknowledgements

The authors are grateful to the SC-NMR Laboratory of Okayama University for the NMR measurements.

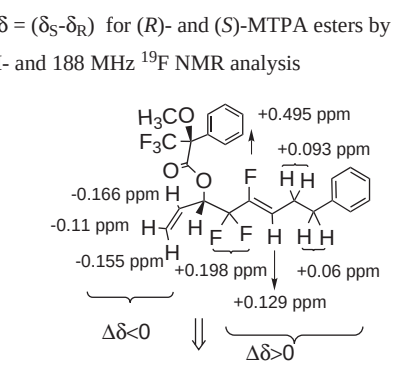


Figure 1. Assignment of the stereochemistry of 8-phenyl-4,4,5-trifluoroocta-1,5-dien-3-ol (**2**).

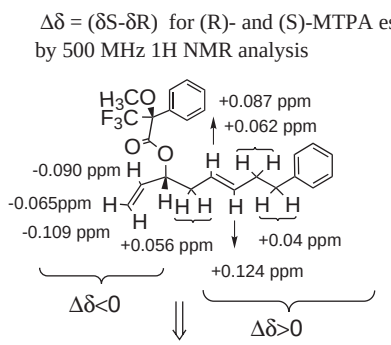


Figure 2. Assignment of the stereochemistry of 8-phenyloct-1,5-dien-3-ol (**5**).

References

1. For reviews, see: (a) Kitazume, T.; Yamazaki, T. *Topics in Current Chemistry*, Springer Verlag, 1997; Vol. 193, pp. 91–130; (b) Percy, J. M. *Top. Curr. Chem.* **1997**, *193*, 131. [2,3]-Wittig rearrangement of difluoroallylic alkoxyacetates, see: (c) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *J. Org. Chem.* **1996**, *61*, 166; (d) Balnaves, A. S.; Gelbrich, T.; Hursthouse, M. B.; Light, M. E.; Palmer, M. J.; Percy, J. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2525; (e) Ito, H.; Sato, A.; Kobayashi, T.; Taguchi, T. *Chem. Commun.* **1998**, 2441 and references cited therein.
2. (a) Itoh, T.; Sakabe, K.; Kudo, K.; Zagatti, P.; Renou, M. *Tetrahedron Lett.* **1998**, *39*, 4071; (b) Itoh, T.; Sakabe, K.; Kudo, K.; Ohara, H.; Takagi, Y.; Kihara, H.; Zagatti, P.; Renou, M. *J. Org. Chem.* **1999**, *64*, 252; (c) Itoh, T.; Kudo, K.; Tanaka, N.; Zagatti, P.; Renou, M. *Enantiomer* **2000**, *5*, in press.
3. Itoh, T.; Kudo, K.; Tanaka, N.; Sakabe, K.; Takagi, Y.; Kihara, H. *Tetrahedron Lett.* **2000**, *41*, 4591.
4. We adapted this nomenclature to discuss the stereochemistry of [2,3]-Wittig rearrangements. (*E*)* and (*Z*)* correspond to (*Z*) and (*E*), respectively. Because the fluorine atom is superior to the carbon atom, this nomenclature does not follow the IUPAC rule.
5. Takagi, Y.; Nakatani, T.; Itoh, T.; Oshiki, T. *Tetrahedron Lett.* **2000**, *41*, 7889.
6. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic (MTPA) esters of (*S*)-**2** showed negative chemical shift differences ($\Delta\delta = \delta S - \delta R$) for protons on C-1 and C-2, while positive chemical shift differences ($\Delta\delta = \delta S - \delta R$) were observed for fluorine atoms on C-4 and C-5, and for protons on C-8 (Fig. 1). Following the same procedure, absolute configuration of (*R*)-**5** was determined as illustrated in Fig. 2.
7. Interestingly, no deuterium analogue of the starting allylic ether was obtained when the reaction was quenched by addition of an excess amount of D_2O, CD_3OD or DCl/D_2O after base treatment. We thus assume that lithiated species TS1 has a very short lifetime, though it is possible to explain the stereoselectivity of the present [2,3]-Wittig rearrangement by the differences of stability between TS1 and TS1′. Because MO (PM3) calculation suggests that the (*S*,*S*)-*endo* form (TS1) is more stable than the (*S*,*R*)-*exo* form (TS1′), if such an equilibrium does exist between TS1 and TS1′, it seems to lie far from TS1, and thus (*E*)*-(*S*)-**2** was obtained as a sole product. MacSpartan Pro was employed for MO (PM3) calculation. Results of MO (PM3) calculation (Heat of formation): (*S*,*R*)-*endo* (TS1); −93.959 Kcal/mol, (*S*,*R*)-*exo* (TS1′); −90.813 Kcal/mol.
8. Brookes, P. C.; Murphy, P. J.; Sommer, K.; Hibbs, D. E.; Hursthouse, B. A.; Malik, K. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1899.
9. For the mechanism of [1,2]-Wittig rearrangement, a radical pathway mechanism is widely accepted. For a review, see: Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 763. Recently Tomooka and Nakai proposed details of the radical mechanism of [1,2]-Wittig rearrangement: Tomooka, K.; Inoue, T.; Nakai, T. *Chem. Lett.* **2000**, 418.
10. Yamazaki, T.; Haga, J.; Kitazume, T.; Nakamura, S. *Chem. Lett.* **1991**, 2171.
11. (a) Morizawa, Y.; Yasuda, A.; Uchida, K. *Tetrahedron Lett.* **1986**, *27*, 1833; (b) Hanamoto, T.; Fuchikami, T. *J. Org. Chem.* **1990**, *55*, 4969; (c) Qian, C.-P.; Nakai, T.; Dixon, D. A.; Smart, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 4602 and references cited therein and in Ref. 1a.