Pergamon

Tetrahedron Letters, Vol. 38, No. 7, pp. 1215-1218, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00020-8

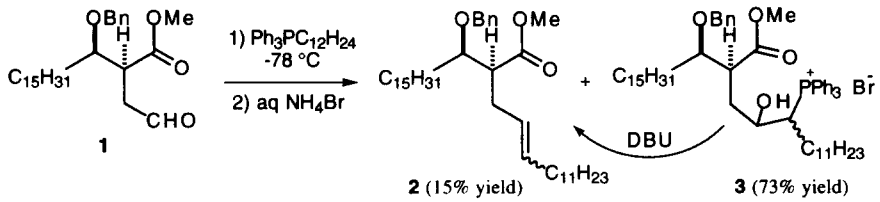
Mechanism and Stereoselectivity of Indirect Wittig Reaction via Isolation of 1,2-Hydroxyphosphonium Salt

Mugio Nishizawa,* Yasuko Komatsu, Dulce M. García, Yohko Noguchi, Hiroshi Imagawa, and Hidetoshi Yamada

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, Japan

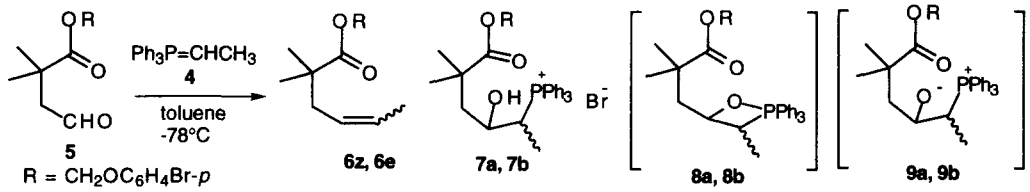
Abstract: An indirect Wittig reaction via isolation of a 1,2-hydroxyphosphonium salt and subsequent treatment with a base such as DBU showed identical stereoselectivity with the corresponding direct Wittig reaction at least between an aliphatic aldehyde and an unstable ylide. The mechanism of the indirect Wittig reaction is discussed on the basis of a synchronous [2+2] mechanism of the Wittig reaction.

The mechanism and stereoselectivity of the Wittig reaction have been studied intensively.[1-12] Recently, Vedejs and Peterson concluded that 1,2-oxaphosphetane is the sole intermediate of the Wittig reaction formed by a synchronous [2+2] mechanism, and the stereoselectivity of the olefinic product is controlled kinetically via an early transition state.[1] However, the mechanism and stereoselectivity of an indirect Wittig reaction via isolation of a 1,2-hydroxyphosphonium salt are not yet fully understood. During the course of our synthetic program dealing with a biologically active glycolipid, TDCM, we have carried out the Wittig reaction of aldehyde **1** and an unstable ylide at -78 °C to prevent partial elimination, leading to an α, β-unsaturated ester.[13] However, the normal Wittig product **2** was obtained only in 15 % yield, and a 1,2-hydroxyphosphonium salt **3** was isolated as the major product in 73% yield. Upon treatment with DBU, Et_3N, or even CH_2N_2, **3** afforded olefin **2** in high yield; thus, the synthetic program itself was not damaged.



We have been interested in the mechanism of the basic transformation of **3** to **2**, and planned to analyze it by the reaction of a salt-free ylide **4** and a simple model aldehyde **5**. Herein we wish to describe that 1,2-hydroxyphosphonium salts **7a** and **7b** (hereafter **7ab**), isolated by a hydrolysis of 1,2-oxaphosphetane intermediates **8ab**, are smoothly converted to olefins **6z** and **6e** (hereafter **6ze**) by treatment with DBU in identical stereoselectivity with the corresponding direct Wittig reaction. Although the betaine is not the intermediate of the Wittig reaction,[9-11] existence of a route from betaine **9ab** to 1,2-oxaphosphetane **8ab** is herein proved again.[8] The stereoselectivity is controlled kinetically at the initial [2+2] cycloaddition step even in the indirect Wittig reaction; thus, the same selectivity is also reflected in the isomer ratio of the 1,2-

hydroxyphosphonium salts **7ab**.



The Wittig reaction of a salt-free ylide **4** with an aldehyde **5** was achieved in toluene at -78 °C for 5 min and then warming up to room temperature gave olefins **6ze** in 73% yield. The *Z/E* ratio was 93:7 based upon GC analysis (entry 1 of Table I). The reaction of **4** and **5** in toluene at -78 °C for 5 min and addition of aqueous ammonium bromide at the same temperature afforded 1,2-hydroxyphosphonium salts **7ab** in 90% yield after column chromatography.[14] The isomer ratio is estimated to be 92:8 based upon the pair of double doublets of secondary methyl signals at δ 1.51 ($J_{P\text{-}H}$ = 19.5 Hz and $J_{H\text{-}H}$ = 7.1 Hz) due to the major isomer and 1.39 ($J_{P\text{-}H}$ = 18.5 Hz and $J_{H\text{-}H}$ = 7.1 Hz) due to the minor isomer.[15, 16] Treatment of the mixture of **7ab** with 1.1 equiv of DBU in THF at room temperature also afforded olefins **6ze** in 81% yield and the ratio was 95:5 (entry 2). By using THF as solvent, the Wittig reaction of **4** and **5** took place in identical yield and identical selectivity (entry 3), and basic treatment of salts **7ab** in toluene-THF (1:2)[17] also afforded olefins **6ze** in the same ratio (entry 4). Thus, the solvent effect on the direct and indirect Wittig reactions is shown to be negligible at least between toluene and THF.

Related aldehydes **10** and **13** were also treated with **4** at -25 °C to give olefins **11ze** and **14ze**, respectively. When the reaction mixture was quenched at -78 °C, the corresponding 1,2-hydroxyphosphonium salts **12ab** and **15ab** were obtained, respectively. Treatment of **12ab** and **15ab** with DBU afforded olefins **11ze** or **14ze**, respectively, and the *Z/E* ratio of each was identical with that of the direct Wittig reaction. These results are also summarized in Table I (entry 5-8) indicating that the indirect Wittig reaction via isolation of 1,2-hydroxy-phosphonium salt shows identical stereoselectivity with the corresponding Wittig reaction.

Therefore, the *Z/E* ratio of the indirect Wittig reaction was identical with not only the direct Wittig reaction but also the isomer ratio of the corresponding 1,2-hydroxyphosphonium salt. According to Vedejs, the 1,2-oxaphosphetane is the sole intermediate of the Wittig reaction and formed by a synchronous [2+2] mechanism based upon extensive experimental[2-11] and theoretical aspects.[12] The formation of 1,2-hydroxyphosphonium salts **7ab**, **12ab**, and **15ab** is through a simple hydrolysis of the corresponding 1,2-oxaphosphetane intermediates such as **8ab**, that are stable at -78 °C as indicated by nmr experiment.[5, 9] Upon treatment of the 1,2-hydroxyphosphonium salts **7ab**, **12ab**, or **15ab** with DBU or even CH_2N_2, acidic OH proton should be abstracted leading to genuine betaine such as **9ab**. Either cyclization of the betaines **9ab** to give 1,2-oxaphosphetanes **8ab** directly or fragmentation to give ylide **4** and aldehyde **5** (and following 2+2 recombination) is possible. When the DBU treatment of **7ab** was carried out in the presence of 50 equiv of propanal, none of the cross-coupling products were detected. Thus, the possibility of the fragmentation-recombination process is excluded, and the formation of the 1,2-oxaphosphetane intermediates **8ab** is a result of the recyclization of the genuine betaines **9ab**.

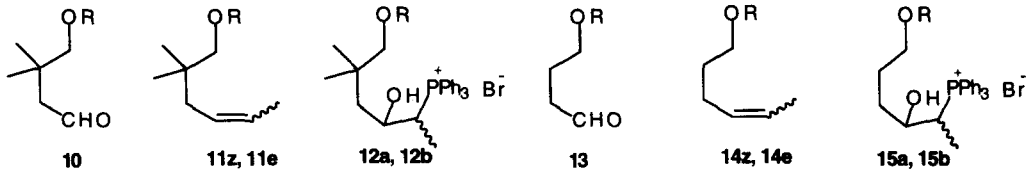
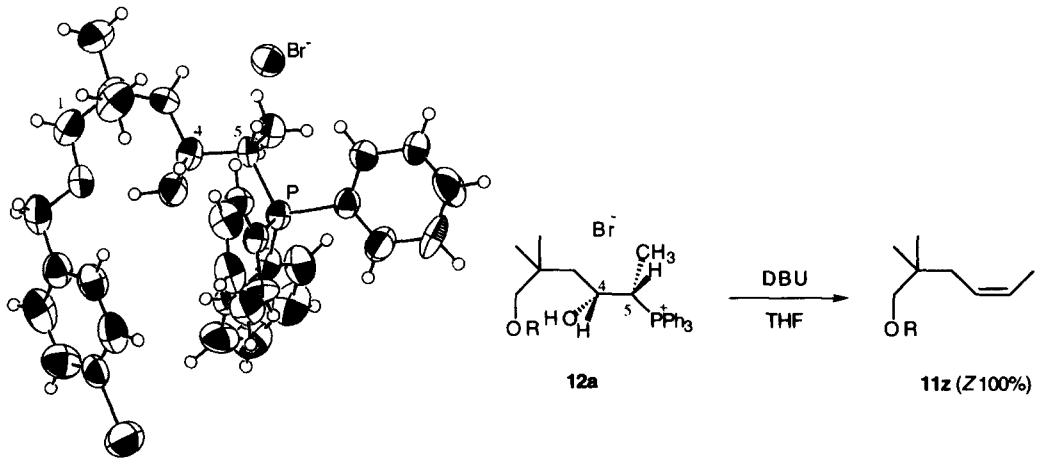


Table I. Direct and indirect Wittig reaction to give *Z* and *E* olefins.

Entry	Starting material	Solvent	Olefins	Yield (%)	*Z/E* ratio
1	**5**	toluene	**6z, 6e**	73	93:7[a]
2	**7a, 7b**	THF	**6z, 6e**	81	95:5[a]
3	**5**	THF	**6z, 6e**	83	93:7[a]
4	**7a, 7b**	toluene-THF (1:2)	**6z, 6e**	87	95:5[a]
5	**10**	toluene	**11z, 11e**	90	88:12[a]
6	**12a, 12b**	THF	**11z, 11e**	79	87:13[a]
7	**13**	toluene	**14z, 14e**	100	89:11[b]
8	**15a, 15b**	THF	**14z, 14e**	77	87:13[b]

[a] Determined by GC analysis using Finnigan 9001 instrument with TC-1 column (30 m x 0.25 μm).
[b] Determined by 600 MHz ^{1}H NMR analysis.

Conformation of the 1,2-hydroxyphosphonium salt is a remaining point of interest. Since the major isomer of **12ab** afforded single crystals from hexane and chloroform, the structure **12a** was confirmed by an X-ray diffraction study.[18] As seen in the perspective drawing, **12a** takes 4*R**5*S** configuration and is expected to yield *Z* olefin. As is the case, purified crystals prepared by repeated recrystallizations (mp 84-86 °C) provided only *Z* olefin **11z** by the treatment with DBU in THF. These results are the definitive evidence that the stereoselectivity of the indirect Wittig reaction is controlled at the initial [2+2] cycloaddition stage forming that 1,2-oxaphosphetane intermediate.



Perspective Drawing of 12a

Acknowledgment: This study was financially supported by Japan Private School Promotion Foundation.

References and Notes

1. Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1
2. Schlosser, M. *Angew. Chem. Internat Ed. Engl.* **1968**, *7*, 650.
3. Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822.
4. Vedejs, E.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1973**, *95*, 5778.
5. Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823.
6. Vedejs, E.; Fang, H. W. *J. Org. Chem.* **1984**, *49*, 210.
7. Vedejs, E.; Marth, C. F.; Ruggeri, R. *J. Am. Chem. Soc.* **1988**, *110*, 3940.
8. Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1988**, *110*, 3948.
9. Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1990**, *112*, 3905.
10. Vedejs, E.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 1985.
11. Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, Jr. H. R.; Whittle, R. R.; Olofson, R. A. *J. Am. Chem. Soc.* **1986**, *108*, 7664.
12. Volatron, F.; Eisenstein, O. *J. Am. Chem. Soc.* **1987**, *109*, 1.
13. Nishizawa, M.; Garcia, D. M.; Minagawa, R.; Noguchi, Y.; Imagawa, H.; Yamada, H.; Watanabe, R.; Yoo, Y. C.; Azuma, I. *Synlett*, **1996**, 452.
14. Structure was confirmed on the basis of ^{1}H NMR, ^{13}C NMR, IR, and FAB MS spectrum.
15. Stereochemical assignments of **7a** and **7b** are difficult from nmr spectra of the mixture of **7ab**.
16. Gray, G. A.; Cremer, S. E.; Marsi, K. L. *J. Am. Chem. Soc.* **1976**, *98*, 2109.
17. Salts **7ab** are insoluble in toluene.
18. The X-ray diffraction study was carried out by Mac Science MXC18 diffractometer, and all diagrams and calculations were performed using CRYSTAN (Mac Science, Japan). Crystal was monoclinic $P2_1$, a = 10.172(3)Å, b = 22.971(6)Å, c = 9.689(2)Å, β = 116.54(2)°, Z = 2, D_{calc} = 1.239 Mg^{-3}, and final R value was 0.045 for 2249 reflections.

(*Received in Japan* 25 *November* 1996; *revised* 19 *December* 1996; *accepted* 25 *December* 1996)