Pergamon

Tetrahedron Letters 43 (2002) 2449–2453

TETRAHEDRON
LETTERS

Co-operative *ortho*-effects on the Wittig reaction. Interpretation of stereoselectivity in the reaction of *ortho*-halo-substituted benzaldehydes and benzylidenetriphenylphosphoranes

Eoin C. Dunne, Éamonn J. Coyne, Peter B. Crowley and Declan G. Gilheany*

Chemistry Department, Conway Institute of Biomolecular and Biomedical Sciences, University College Dublin, Belfield, Dublin 4, Ireland

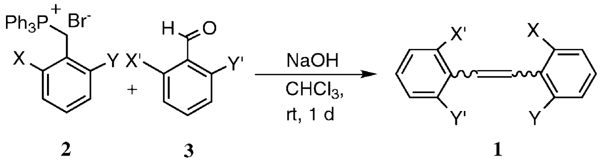
Received 5 December 2001; revised 28 January 2002; accepted 6 February 2002

Abstract—The *E*/*Z* ratios of the stilbenes **1** formed in the Wittig reaction of *ortho*-halo substituted benzyltriphenylphosphonium salts **2** and benzaldehydes **3** were determined. It was found that there is a co-operative effect of one *ortho*-halo group on each of the two reacting partners which increases *Z*-selectivity, but two such groups on the same reactant gives high *E*-selectivity. The effects are strong enough to be preparatively significant in certain cases and can be interpreted within the modern framework of the Wittig mechanism established by Vedejs and co-workers. © 2002 Elsevier Science Ltd. All rights reserved.

The Wittig reaction[1] is one of the most important and synthetically useful reactions in organic chemistry.[2] It has also attracted much attention and controversy regarding its mechanism.[2a] Wittig originally proposed[1] that the reaction proceeds via an oxaphosphetane (OPA) but this idea fell into disfavor until the work of Vedejs.[3] For unstabilized[4] ylides, it is now accepted[3,5] that OPAs are the intermediates in the reaction and the transition states for OPA formation have been carefully analyzed.[3b,e,6,7] The situation is less clear for semi-stabilized ylides because the OPAs are much harder to detect, having only transient existence.[3c] Thus, OPAs have been detected with alkyl-substituted aldehydes[3c] but not with benzaldehydes as the reacting partner.[5a]

An especially important test applied to any mechanistic proposal for the Wittig reaction has been its explanation of the *Z*/*E* ratio of the alkene products. Recently we required small amounts of a series of *E*- and *Z*-stilbenes of the type **1** where there is at least one *ortho*-halo substituent on one or both rings. We chose to make them by Wittig reactions, with subsequent chromatographic separation, from the corresponding substituted benzyltriphenylphosphonium salts **2** and benzaldehydes **3** with sodium hydroxide (Scheme 1). During the work some curious trends in the *E*/*Z* selectivity were noted. We found these could be interpreted on the basis of intermediate OPAs, thereby providing support for their involvement in the mechanism.

Benzylidenetriphenylphosphorane gives almost no selectivity with benzaldehyde.[2] However, substitution on both the ylide and aldehyde components can shift the selectivity in either direction, sometimes in an apparently inexplicable manner.[2c] In addition, *ortho* substitution is known to affect reactions at phosphorus.[8] In the Wittig reaction, McEwen and Cooney[9] showed that *ortho*-methoxy substituents on the aryl rings attached to phosphorus cause greater *E*-selectivity in reactions with a range of *para*- and *meta*-substituted benzaldehydes, while similar placement of methoxymethyleneoxy groups causes preparatively useful *Z*-selectivity in Wittig reactions of stabilized ylides.[10] More relevant to our work were reports by Cushman et al.[11] and Yamataka et al.[7] that *ortho*-methoxy and halo substituted benzaldehydes gave predominately *Z*-stilbenes in reaction with benzylidenetriphenylphosphorane. Yamataka and co-workers[7] proposed that this selectivity was due to a



Scheme 1.

Keywords: Wittig reaction; *E*/*Z* ratios; stilbenes; co-operative effect.

* Corresponding author. Tel.: +353-1-7162308; fax: +353-1-7162127; e-mail: declan.gilheany@ucd.ie

PII: S0040-4039(02)00281-2

chelating interaction of filled p-orbitals on the substituent and the carbonyl oxygen to the phosphorus atom in an initial σ-complex of aldehyde and ylide. Similar explanations had been advanced to explain the *ortho* effects in other reactions at phosphorus.[8] We were interested in exploring the full extent of the *ortho* effect and also the effect of similar substitution on the benzylidenetriphenylphosphorane partner, which ordinarily is expected to produce the opposite effect.[2c,7]

Table 1 shows results from the reaction in chloroform of substituted benzyltriphenylphosphonium salts with benzaldehydes in the presence of aqueous NaOH (50% w/v, 5 equiv.) at ambient temperature.[12] This simple two-phase reaction medium can be used because the phosphonium salt itself acts as a phase transfer agent. It was gratifying that the yields and selectivity[13] were somewhat greater than those reported by Yamataka et al.[7] using NaHMDS as base. After most of this work was complete Hwang et al.[14] published a related study[15] in dichloromethane using much more dilute NaOH solution (0.1 M, 1 equiv.) which gave higher yields. Somewhat better selectivity has been reported[16] in a similar system by the use of solid KOH and crown ether catalysis at low temperature. Because different reaction conditions were used, exact comparisons with previous work are inappropriate.[17] On the other hand qualitative conclusions can be drawn regarding the influence of the *ortho*-halo substituents.

From Table 1 it can be seen that there is the expected[7] pronounced effect of the placement of one *ortho*-halo substituent on the aldehyde such that the proportion of *Z*-alkene is increased (compare entries **8**, **1**, **10**, **19**). More interesting is that placement of an *extra* halo substituent on the salt partner *increases* the proportion of *Z*-isomer (compare entries **1**/**3**, **10**/**12**, **19**/**21**), despite the fact that placement of a single halo substituent on the salt normally leads to a greater proportion of *E*-isomer (compare entries **8**, **2**, **11**, **20**). We discuss the origin of this co-operative *ortho* effect below. The placement of a second *ortho*-substituent on the same reacting partner leads to a substantial increase in the *E*-isomer proportion (compare entries **1**/**5**, **10**/**14**, **2**/**4**, **11**/**13**). However the co-operative effect can still be discerned because when the third halo substituent is added the *Z*-isomer proportion increases again (compare entries **4**/**7**, **5**/**6**, **13**/**16**, **14**/**15**). Finally when all four *ortho* positions are occupied the *E*-isomer is predominant (entry **17**). We speculate that this outcome reflects the much greater steric crowding introduced. The co-operative effect is not dependent on the halogens being the same and hence is not a regular electronic effect through the aromatic rings (entries **22**/**23**).

The detailed course of the Wittig reaction, as established by Vedejs and co-workers[3b,e] for salt-free unstabilized and some semistabilized ylides, is as follows. It proceeds by an asynchronous [2+2] cycloaddition[18] to an oxaphosphetane (OPA) containing a pentavalent trigonal bipyramidal phosphorus atom. The OPA then rapidly decomposes to the alkene and phosphine oxide. Therefore, the formation of OPA is overall rate determining[3c,e] and the *Z*/*E* ratio observed in the final product reflects the ratio of *cis*/*trans* OPAs produced in the first step.[3b,e,19] Normally the *cis*-OPA is considered to be the higher energy form.[3b,e] However, there is usually kinetic control in OPA-formation[3e,19] so *cis*-OPA can be formed in excess if the TS leading to it has the lower energy. It is proposed[3c,e] that unstabilized ylides will have an early transition state which will be reactant-like and therefore non-planar with 1,3-interactions dominant, leading to a *cis*-orientation and thence *Z*-alkene, Fig. 1(a). Stabilized ylides will have a late transition state, be product-like and therefore planar with 1,2 interactions dominating, leading to a *trans*-OPA and the *E*-alkene, Fig. 1(b). Semi-stabilized ylides are proposed to be more like unstabilized ylides but there is insufficient data to be sure.[3b] Note that, since the reaction of the ylide is nucleophilic in nature, electron-withdrawing substituents on the aldehyde should speed up the reaction, whereas on the salt they should slow down the reaction.[7]

Table 1. Results of the Wittig reaction[a] between *ortho*-substituted benzyltriphenylphosphonium bromides **2** and substituted benzaldehydes **3** to give *Z*- and *E*-substituted stilbenes **1**,[b] according to Scheme 1

Entry	Salt	Ald	*Z*:*E*	Entry	Salt	Ald	*Z*:*E*	Entry	Salt	Ald	*Z*:*E*
1	H	2-F	70:30	**10**	H	2-Cl	77:23	**19**	H	2-Br	85:15
2	2-F	H	26:74	**11**	2-Cl	H	23:77	**20**	2-Br	H	50:50
3	2-F	2-F	90:10	**12**	2-Cl	2-Cl	87:13	**21**	2-Br	2-Br	95:5
4	2,6-F	H	14:86	**13**	2,6-Cl	H	1:99	**22**	2-F	2-Br	95:5
5	H	2,6-F	9:91	**14**	H	2,6-Cl	5:95	**23**	2-Br	2-F	95:5
6	2-F	2,6-F	23:77	**15**	2-Cl	2,6-Cl	25:75				
7	2,6-F	2-F	25:75	**16**	2,6-Cl	2-Cl	40:60	**24**	2-Me	2-Cl	90:10
								25	2-Cl	2-Me	70:30
8	H	H	40:60	**17**	2,6-Cl	2,6-Cl	1:99	**26**	H	2-Me	57:43
9[b]	H	H	61:39	**18**[b]	H	2-Cl	95:5	**27**	2-Me	H	67:33

[a] Experimental procedure in Ref. 12.

[b] Unspecified substituents are H. The substituted benzylidenetriphenylphosphonium chloride was used.

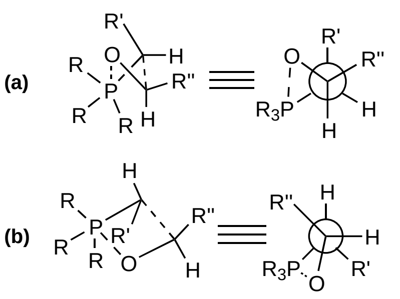
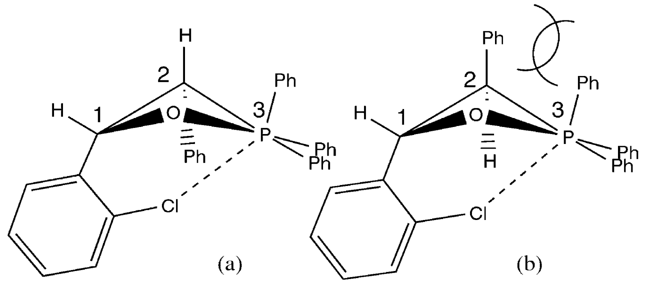


Figure 1. (a) The puckered transition state leading to *cis*-OPA; (b) The planar transition state to *trans*-OPA adapted from Ref. 2a.

Enhanced Z-selectivity requires that a greater amount of *cis*-OPA be produced. This could be achieved by: (a) factor(s) which render the *cis*-OPA the lower energy form; (b) factor(s) which stabilize the TS leading to *cis*-OPA or destabilize that to the *trans*; (c) factor(s) which further encourage an early TS. We propose that the *ortho*-effects operate on the OPAs themselves (point a). We utilize the proposal of Yamataka et al.[7] that an *ortho* halo substituent on the aldehyde is capable of bonding to phosphorus. However we propose that this effect simply operates to give a more (or less) stable *cis*-OPA, rather than in the initial σ-complex between carbonyl oxygen and phosphorus as they proposed. There will also be electronic effects of halo-substitution on the rate of reaction.[20]

A halo-substituent *on the aldehyde* (i) speeds up reaction[7] thereby encouraging an earlier TS and (ii) if at the *ortho*-position, can bond to phosphorus,[21] thereby stabilizing the OPAs. Of the four possible OPAs, *cis*- and *trans*- with and without halogen bonding, we assume that the halogen-bonded forms (Fig. 2) are of lower energy. Examination of molecular models leads us to believe that the *cis*-OPA with halogen bonding is actually less crowded than the corresponding *trans*-OPA. The new bonding interaction is facilitated by puckering of the four-membered ring to enable a closer approach of the *ortho*-substituent to the now octahedral phosphorus. The puckering in turn stabilizes the *cis*-OPA (Fig. 2a) by reducing the unfavorable 1,2-interactions. More importantly, the *trans*-OPA is destabilized by an unfavorable 2,3-interaction (Fig. 2b). Placement of an *ortho*-halo substituent *on the salt* is expected to slow the reaction, due to its electronic effect,[7] giving more E-alkene as observed. A halogen bonding interaction to phosphorus is possible but the bonding distance is rather long.



(a) (b)

Figure 2. Bonding of an *o*-chloro substituent to phosphorus in (a) the *cis*-OPA and (b) the *trans*-OPA.

There are three scenarios for placement of two *ortho*-substituents. (1) One each on salt and aldehyde: the unfavorable 1,2-interaction in the halogen-bonded *cis*-OPA (Fig. 2a) is increased a little but there is additional steric crowding in the already crowded *trans*-OPA (Fig. 2b), thereby enhancing Z-selectivity. Thus, we are proposing a steric effect of the *ortho*-halo substituent on the salt which co-operates with the through space electronic effect of the *ortho*-substituent on the aldehyde. (2) Both on aldehyde: this has the same small detrimental effect on the *cis*-OPA (Fig. 2a) but almost no effect on the *trans*-OPA, which leads to higher E-selectivity. It is this latter result, which leads us to propose the operation of halogen bonding in the OPA because it cannot be explained on the basis of chelation in the initial σ-complex. (3) Both on the salt: this simply reinforces the expected E-selectivity.

To explore these ideas a little, we placed a methyl group as second *ortho*-substituent on the salt. We expected that its steric bulk would enhance Z-selectivity by making the *trans*-OPA even more crowded. This was not a perfect test because the methyl group itself is somewhat Z-selective (entries **8**/**26**/**27**), but it did indeed give the same effect as chloro (compare entries **12**/**24**). Interestingly switching the methyl and chloro groups still produced a co-operative effect at a lower level (compare entries **24**/**25**). This may be related to the possibility of weak halogen bonding from the *ortho*-position on the salt.

We have shown that there are consistent effects of multiple *ortho*-halo substituents on the Wittig reaction to produce stilbenes. They can be rationalized within the mechanistic framework of the reaction developed by Vedejs and co-workers.[3a] It is now possible to predict which combination of substituents will be synthetically useful in most cases. Taken together with the known[2c] Z-selectivity of the chloride counterion (entries **8**/**9**, **10**/**18**), either E- or Z-isomer can be predictably synthesized in good yield in certain defined cases as shown in Chart 1.

Acknowledgements

We acknowledge support from Enterprise Ireland (Grant SC/96/429 and Studentship for E.C.D.). E.C.D. also thanks University College Dublin for a Demonstratorship.

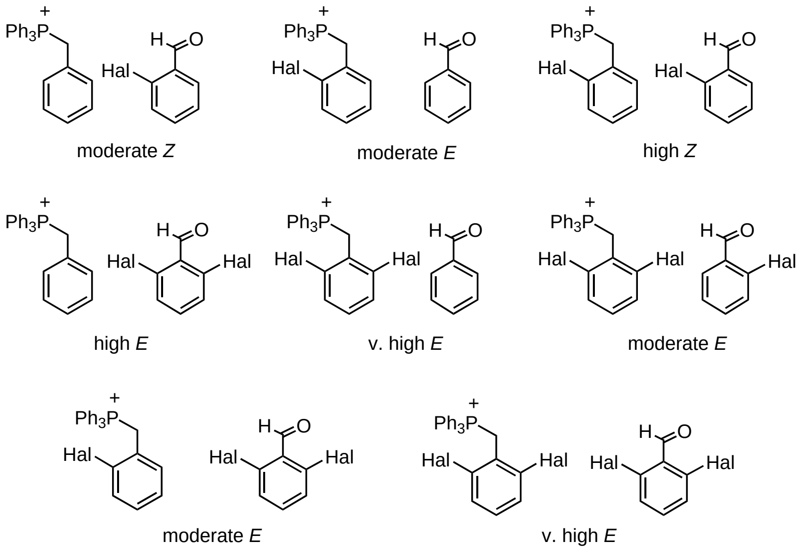


Chart 1. Approximate selectivities in the Wittig reaction to give *ortho*-halo substituted stilbenes: moderate: 70–85; high: 85–95; very high: 95–99%

References

1. Wittig, G.; Geissler, G. *Justus Liebigs Ann. Chem.* **1953**, *580*, 44.
2. (a) Johnson, A. W. *Ylides and Imines of Phosphorus*; Wiley: NY, 1993; Chapters 8 and 9, pp. 221–305; (b) Kolodiazhnyi, O. I. *Phosphorus Ylides*: *Chemistry and Application in Organic Synthesis*; Wiley: New York, 1999; (c) Gosney, I.; Rowley, A. G. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press, 1979; Chapter 2, pp. 17–153.
3. (a) Vedejs, E.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1973**, *95*, 5778; (b) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1988**, *110*, 3948; (c) Vedejs, E.; Fleck, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 5861; (d) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1990**, *112*, 3905; (e) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1.
4. Stabilized ylides have a carbonyl or similar group conjugated to the P=C bond. Semi-stabilized (moderated) ylides have phenyl or similar group and unstabilized have no such groups.
5. (a) Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R.; Whittle, R. R.; Olofson, R. A. *J. Am. Chem. Soc.* **1986**, *108*, 7664; (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
6. (a) Yamataka, H.; Nagase, S. *J. Am. Chem. Soc.* **1998**, *120*, 7530; (b) Yamataka, H.; Takatsuka, T.; Hanafusa, T. *J. Org. Chem.* **1996**, *61*, 722; (c) Yamataka, H.; Nagareda, K.; Takatsuka, T.; Ando, K.; Hanafusa, T.; Nagase, S. *J. Am. Chem. Soc.* **1993**, *115*, 8570.
7. Yamataka, H.; Nagareda, K.; Ando, K.; Hanafusa, T. *J. Org. Chem.* **1992**, *57*, 2865.
8. (a) McEwen, W. E.; Janes, A. B.; Knapczyk, J. W.; Kyllingstad, V. L.; Shiau, W.-I.; Shore, S.; Smith, J. H. *J. Am. Chem. Soc.* **1978**, *100*, 7304–7311 and references cited therein; (b) Keldsen, G. L.; McEwen, W. E. *J. Am. Chem. Soc.* **1978**, *100*, 7312–7317.
9. McEwen, W. E.; Cooney, J. V. *J. Org. Chem.* **1983**, *48*, 983.
10. Zhang, X.; Schlosser, M. *Tetrahedron Lett.* **1993**, *34*, 1925.
11. Cushman, M.; Nagarathnam, D.; Gopal, D.; Chakraborti, A. K.; Lin, C. M.; Hamel, E. J. *J. Med. Chem.* **1991**, *34*, 2579–2588.
12. Experimental procedure: the bromide (0.020 mol) and benzaldehyde (0.020 mol) were dissolved in chloroform (150 cm^3) and 50% w/v aqueous NaOH (8.8 cm^3; 0.100 mol) added to the rapidly stirring solution. The ylidic color was noted shortly after addition and gradually faded. Stirring was maintained overnight, after which the layers were separated, the organic washed with water (3×50 cm^3) and dried over $MgSO_4$. The chloroform was evaporated and a ^1H NMR spectrum ($CDCl_3$, 300 MHz) taken of the resulting crude oil. Treatment with pet. spirit (40–60°C) (100 cm^3) caused triphenylphosphine oxide to precipitate and the solid was washed with 4–6 portions of pet. spirit (40–60°C) (50 cm^3) to remove all the stilbene. These washings were combined and the solvent evaporated to give an oil (generally yellow) which often crystallized slowly on standing. The yield at this point was >70%, except entries **8**=60, **11**=61, **17**=59, **6**=52, **2**=67%. Separation of the isomers was achieved using flash chromatography on neutral alumina with elution by pentane. The *E*/*Z* ratios were then calculated by comparing the alkene peaks of the isomers in the crude ^1H NMR. Yields quoted are of the crude stilbene. All reduced yields were accounted for by the remaining aldehyde and in some cases hydrolysis of the phosphonium salt or ylide to give the substituted toluene was noted. No other products were detected. The aldehydes were checked for the presence of the carboxylic acid prior to use (Ref. 3e).
13. Great care had to be taken to determine the correct *Z*/*E* ratio because of isomerization on chromatography. Even on neutral alumina, we noted isomerization leading to loss of the *Z*-isomer on chromatography in a number of cases with *Z*-2,2′-difluorostilbene being especially prone. This sensitivity presented some difficulty in obtaining the data for entry **3** because there was almost complete

conversion to the *E*-isomer on chromatography. *Z*-2,2′-Difluorostilbene was also sensitive to light in the same way and so separation of the isomers was carried out by very careful fractional recrystallization in the dark, from pet. spirit (40–60°C). The *E*-isomer was found to be least soluble and could be filtered from the cooled solution. The *Z*-isomer gradually crystallized from solution as large clear prisms when kept in the freezer but dissolved again at room temperature.

14. Hwang, J.; Lin, R.; Shieh, R.; Jwo, J. *J. Mol. Cat.* **1999**, 125.
15. Several of the substrates studied by Hwang et al. are the same as entries in Table 1 but in most cases they report lower *Z*-selectivities and higher yields. We repeated one of these, entry **24**, using their method but with our work-up procedure and found no change in selectivity (90:10). However, there were no hydrolysis products, which accounts for their increased yield. We think that the lower selectivities recorded by Hwang et al. are due to alkene isomerization during their chromatographic work-up procedure (see Ref. 13).
16. Belluci, G.; Chiappe, C.; Lo Moro, G. *Tetrahedron Lett.* **1996**, *24*, 4225.
17. Wittig reactions with benzylides are unusually sensitive to temperature (see Refs. 3e,7), which we have not controlled rigorously. However the reaction procedure was consistent, room temperature was always in the range 20–25°C and we have used a relatively large volume of solvent which should moderate any exotherms. We checked that there were no large temperature rises on addition for the most reactive ylide/aldehyde pairs
18. There may be an initial electron transfer step, see Ref. 6.
19. There are a small number of exceptions to this scheme in certain defined circumstances, see Refs. 3b,e and 5.
20. Although the energy differences of the non-bonding interactions we will discuss are small, they are similar to those governing ee in asymmetric synthesis, consideration of which has been a highly effective tool in the latter activity.
21. The bonding will be from a lone pair on halogen to a suitable acceptor orbital on phosphorus hence the bond angle of <180° shown in Fig. 2. The likely acceptor orbital is a hybrid antibonding combination which we have shown is unlikely to involve any d orbital contributions: see, Gilheany, D. G. *Chem. Rev.* **1994**, *94*, 1339.