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STEREOCHEMICAL OBSERVATIONS ON THE WITTIG REACTION OF OXIDO PHOSPHONIUM YLIDES WITH ALDEHYDES[†]

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Abstract: The reaction of aldehydes with oxido ylides shows a dramatic dependence of alkene stereochemistry on the distance between oxygen and phosphorus atoms; ylides with proximal O and P atoms favor production of *E* alkenes. The high *E* stereoselectivity with γ-oxido ylides is not mainly attributable to intramolecular proton-exchange in a Wittig intermediate.

The stereochemistry of alkene formation in the Wittig reaction has attracted widespread interest for many years.[1,2] Although non-stabilized phosphonium ylides generally react with aldehydes to afford largely *Z* alkenes,[1] there are some special exceptions, such as β-oxido[3] and γ-oxido[4] ylides, which exhibit unexpectedly enhanced *E* stereoselectivity. The high *E* stereoselectivity of γ-oxido ylides has been rationalized by internal, base-induced equilibration of a Wittig intermediate ("trans-selective Wittig" mechanism[5]).[4a,4b] This mechanism, which requires proton transfer from carbon to oxygen within the Wittig intermediate (oxaphosphetane/betaine), has been drawn into question by our observations with δ-carboxy ylide **1**:[6] (1) although **1** possesses only a weakly basic carboxylate group, it gives anomalously large amounts of *E* alkenes in reactions with aromatic aldehydes, and (2) the exaggerated production of *E* alkenes with **1** is virtually abolished for aliphatic aldehydes. Also, ε-oxido ylide **2** does not give accentuated amounts of *E* alkene,[7] even though a seven-membered cyclic transition state is suitable for intramolecular proton transfer.[8]

Ø$_3$P=CH(CH$_2$)$_3$COO$^-$M$^+$ **1**

Ø$_3$P=CH(CH$_2$)$_4$O$^-$M$^+$ **2**

Ø$_3$$\overset{+}{P}$(CH$_2$)$_3CH_3$ Br$^-$ **3**

Ø$_3$$\overset{+}{P}$(CH$_2$)$_n$OH Br$^-$ **4** (n = 2-5,8,11)

(Ø = C$_6$H$_5$)

Because of the usefulness of β- and γ-oxido ylides in the stereoselective synthesis of allylic and homoallylic alcohols,[3,4] we have been investigating this area systematically. We have now studied (1) oxido phosphonium ylides with different distances between the oxido and ylide centers, and (2) an α-deuterio γ-oxido ylide as a mechanistic probe. Notably, our results show a dramatic dependency of alkene stereochemistry on ylide chain length (viz. **4**), and contradict an intrinsic "trans-selective Wittig" mechanism as a major source of the exaggerated *E* stereoselectivity.

A standard procedure was employed to evaluate the reaction of phosphonium ylides with aldehydes. Each hydroxy phosphonium bromide salt (1 mmol), **4a**-**4f**, was treated with lithium

[†] Dedicated to Professor Kurt Mislow on the occasion of his 60th birthday.

hexamethyldisilazide (LHMD, 2.1 mol-equiv) in 3 ml of tetrahydrofuran (THF) at 23°C (15-30 min). Benzaldehyde or hexanal (0.8 mol-equiv) was added, immediately dissipating the ylide color, and the reaction was stirred for 30-60 min.[9] After quenching with water, the alkene products were isolated and analyzed; the *Z*/*E* isomer ratios were determined by GLC.[10]

To establish a reference for comparison, **3** was reacted with benzaldehyde or hexanal under standard conditions (Table): for benzaldehyde the *Z*/*E* ratio was 50:50 (entry 11) and for hexanal it was 82/18 (entry 14). The benzaldehyde reference reaction with lithium pentoxide present gave *Z*/*E* ratios ranging from 53:47 to 63:37 (entries 12 and 13). Thus, such a lithium salt, analogous to the intramolecular salt in oxido ylides, is unable to augment *E* stereoselectivity, either by a lithium-salt effect or, more importantly, by acting as a base in a "trans-selective Wittig" reaction.

Results obtained with ylides from **4**, under the standard and some special related conditions, are presented in the Table. The influence of chain length on reaction stereochemistry for benzaldehyde is obvious, but it can be more readily appreciated from the Figure. Significantly abnormal *E* stereoselectivity ($\geq$20%) was observed with benzaldehyde for oxido ylides from **4a**-**4d** (n ranging from 2 to 5), *E* stereoselectivity being greatest for ylides of short chain length. Fewer experiments were conducted with hexanal, but a similar trend is evident (entries 8-10; Figure). Although *E* stereoselectivity with hexanal is lower relative to benzaldehyde, the enhancement of *E* stereoselectivity for both aldehydes is comparable relative to reference reactions for each.[11]

Abnormal *E* stereoselectivity with ylides bearing nucleophilic groups could be attributed to an internal equilibration of an intermediate betaine/oxaphosphetane.[4a,4b] To explore the applicability of this mechanism, we conducted experiments with two α-deuterated ylides: $\phi_3P{=}CD(CH_2)_2CH_3$ (**5**) and $\phi_3P{=}CD(CH_2)_2O^-Li^+$ (**6**). As a model, ylide **5** was produced in THF from $\phi_3\overset{+}{P}CD_2(CH_2)_2CH_3\ Br^-$ [12] with *n*-butyllithium (1.6 M in hexane, 1.0 mol-equiv), reacted with benzaldehyde at -78°C to form a Wittig intermediate (stirred 20 min), treated with 5 mol-equiv of hexamethyldisilazane (proton source) for 45 min, and rapidly warmed to 60°C to liberate olefin. The olefinic products (*Z*/*E* = 62:38) contained ca. 85% deuterio species by GLC/MS (equally distributed for both isomers), corresponding to a small amount (ca. 15%) of deuterium wash-out by H/D exchange. Using this procedure, with 5 mol-equiv of proton source, ylide **6**[13] was reacted with benzaldehyde to give a mixture of homocinnamyl alcohols (*Z*/*E* = 12:88), each containing ca. 70% D (GLC/MS). If *E* alkene formation with **6** were to require an internal epimerization mechanism, then a statistical distribution of exchangeable H and D (ca. 17% D) should have been realized in the homocinnamyl alcohols. Since residual D content greatly exceeded 17%, an equilibration mechanism does not account for the high *E* stereoselectivity (88% *E*).[14]

Anomalous *E* stereoselectivity is associated not only with the presence of anionic (or nucleophilic) residues in the phosphonium ylide,[6a] but also with the appropriate proximity of the anionic and ylide centers. The anomalous *E* stereoselectivity with oxido ylides does not appear to be principally caused by intramolecular base-promoted epimerization of a Wittig-reaction intermediate. A mechanistic discussion is reserved for a full account of our work.

Table. Wittig Reactions of Oxido Ylides[a]

entry	aldehyde	phosphonium salt	mol-equiv base	*Z*/*E* ratio	isolated yield
1[b]	ϕCHO	**4a** (n = 2)	2.1	28/72	14%
2[c]	ϕCHO	**4a** (n = 2)	2.1	3/97	--
3[d]	ϕCHO	**4b** (n = 3)	2.1	4/96	80
4	ϕCHO	**4c** (n = 4)	2.1	15/85	--
5	ϕCHO	**4d** (n = 5)	2.1	26/74	--
6	ϕCHO	**4e** (n = 8)	2.1	59/41	50
7	ϕCHO	**4f** (n = 11)	2.1	62/38	68
8	hexanal	**4b** (n = 3)	2.1	42/58	82
9[e]	hexanal	**4d** (n = 5)	2.1	83/17	--
10[e]	hexanal	**4f** (n = 11)	2.1	92/8	--
11	ϕCHO	**3**	1.1	50/50[f]	86
12[g]	ϕCHO	**3**	1.1	63/37	87
13[h]	ϕCHO	**3**	1.1	53/47	--
14[e]	hexanal	**3**	1.1	82/18	--

(a) Reactions were performed under standard conditions (23°C) with LHMD, unless otherwise noted. n = number of carbon atoms separating the oxygen and phosphorus atoms. (b) LHMD was added to the phosphonium salt and benzaldeyde at 0°C, because of ylide instability. (c) Conducted with 2.1 mol-equiv of *n*-butyllithium (1.6 M in hexane) according to published procedure (ref 3a, 3b). (d) The γ-oxido ylide was also generated from ϕ_3P=CH$_2$ and ethylene oxide (ref 4); a 4/96 *Z*/*E* ratio was obtained. (e) Analyzed by GLC/MS as the mixture of epoxides (prepared with MCPBA). (f) Four experiments showed a deviation of ±2% in *Z*/*E* ratio. (g) Standard reaction of **3** but 1.0 mol-equiv of lithium pentoxide (from *n*-pentanol and LHMD *in situ*) was present prior to addition of benzaldehyde. (h) Similar to footnote *g*; 5.0 mol-equiv of lithium pentoxide present.

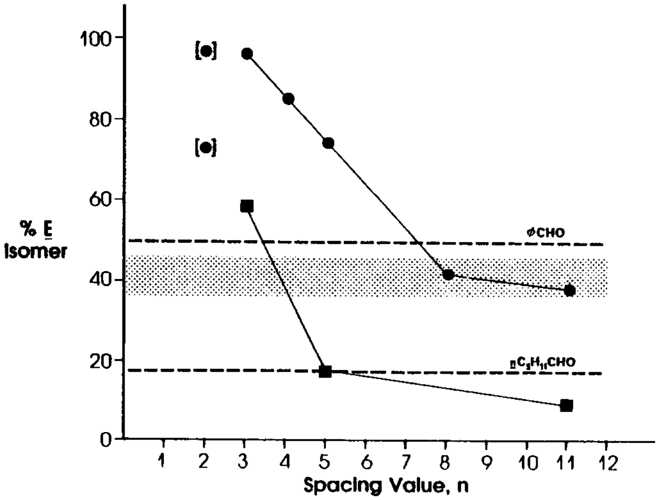

Figure. Variation of *Z*/*E* alkene ratio with distance between O and P atoms in oxido ylides from **4a**-**4f**. Symbols are assigned as follows: ● benzaldehyde reaction, ■ hexanal reaction. The brackets around a data point denote departure from the standard LHMD reaction conditions (see Table). Reference reactions with **3** are indicated by the horizontal dotted lines (entries 11 and 14); reference reactions with ϕCHO, **3**, and added lithium pentoxide are indicated by the shaded area (entries 12 and 13). Lines connecting the data points are present only as an aid to the viewer.

References and Notes

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5. The base-induced "trans-selective Wittig" reaction was first described by Schlosser,[1b] and has been referred to as a "Schlossler-type" process or mechanism.
6. (a) Maryanoff, B. E.; Duhl-Emswiler, B. A. *Tetrahedron Lett.* **1981**, *22*, 4185; (b) It should be noted that the abnormal bias for *E* olefin with **1** is independent of metal ion (Li, Na, K), although *E* stereoselectivity is diminished with Na and K.
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9. Reactions monitored with time showed no change in *E/Z* ratio over the reaction course.
10. Alkene isomer mixtures were analyzed by GLC and GLC/MS. ^{1}H NMR integrations of the vinyl protons gave isomer ratios consistent with those from GLC analysis.
11. γ-Oxido ylides with methyl substitution have afforded us higher *E* stereoselectivities than has the ylide from **4b**, consistent with literature reports on methylated γ-oxido ylides.[4] Discussion of this point will appear in a full paper.
12. (a) Synthesized by reaction of $\emptyset_3P{=}CD_2$ with *n*-propyl bromide; see: Smith, D. J. H., in "Organophosphorus Reagents in Organic Synthesis," J. I. G. Cadogan, Ed., Academic Press, New York, 1979, pp 207-211 and ref 3f. (b) Satisfactory microanalytical and 360-MHz ^{1}H NMR data were obtained for the deuterated phosphonium salt (98+% D content).
13. Generated from $\emptyset_3\overset{+}{P}CD_2(CH_2)_2OH\ Br^-$ and 2 mol-equiv of *n*-BuLi at -78°C. The phosphonium salt was prepared via base-induced deuterium exchange of **4b**.[12b]
14. Similar results were obtained in analogous deuterium exchange experiments with hexanal.

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