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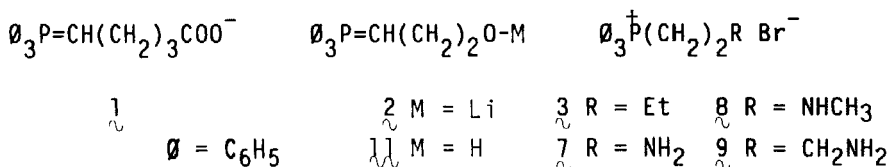
ANOMALOUS STEREOCHEMISTRY IN THE WITTIG REACTION INDUCED BY NUCLEOPHILIC GROUPS IN THE PHOSPHONIUM YLIDE

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Abstract Reaction of ylides from 3-9 with benzaldehyde show that carboxylate and oxido functionalities proximate to the ylide center promote anomalously high \underline{E} stereoselectivity in alkene formation. Through the use of α -deuterated ylides 12-14, an internal "trans-selective Wittig" mechanism was ruled out as a principal source of exaggerated \underline{E} alkene production.

Non-stabilized triphenylphosphonium ylides generally react with aldehydes to afford largely \underline{Z} alkenes.¹ However, there are some special exceptions, such as β -oxido² and γ -oxido³ ylides, which exhibit unexpectedly enhanced \underline{E} stereoselectivity. This has been rationalized for γ -oxido ylides by an internal "trans-selective Wittig" mechanism, which requires proton transfer from carbon to oxygen within the Wittig intermediate (oxaphosphetane/betaine).^{3a,3b} Two observations with δ -carboxy ylide 1 caused us to question such a mechanism:⁴ (1) although 1 possesses only a weakly basic carboxylate group, it gave anomalously large amounts of \underline{E} alkenes in reactions with aromatic aldehydes, and (2) exaggerated production of \underline{E} alkenes with 1 was virtually abolished for aliphatic aldehydes.

We have now systematically studied carboxy, oxido, and amino phosphonium ylides having different distances between the nucleophilic and ylide centers. Our results reveal that abnormal \underline{E} stereoselectivity is maximized when anionic groups are present at certain optimal distances from the ylide site. We also have evidence indicating that an internal "trans-selective Wittig" mechanism is not a major source of anomalous \underline{E} stereoselectivity.

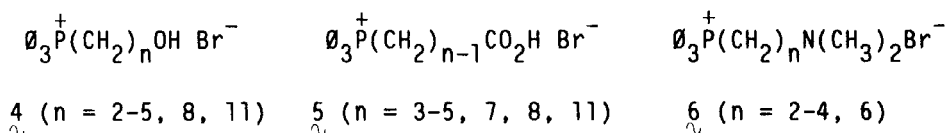


RESULTS AND DISCUSSION

Each phosphonium bromide salt (1 mmol) was treated with lithium hexamethyldisilazide (LHMD), 1.1 mol-equiv, or 2.1 mol-equiv for salts with an auxiliary acidic group, in 3 ml of THF at 23°C (15–30 min). Benzaldehyde (0.8 mol-equiv) was added, immediately dissipating the ylide color; the reaction was stirred for 30–60 min. After quenching with water, the alkene products were isolated and analyzed; Z/E isomer ratios were determined by GLC.

Reference reactions with 3 (Table I) showed that lithium n-hexanoate or lithium n-pentoxide (1 and 5 mol-equiv) are unable to augment E stereoselectivity, either by a lithium-salt effect or, more importantly, by acting as internal bases. Experiments with 4–9 showed a dramatic influence of chain length on stereochemistry (Table I). Significantly abnormal E stereoselectivity (>20%) was observed for oxido ylides from 4 with *n* ranging from 2–5, carboxy ylides from 5 with *n* = 3 to 7, and the dimethylamino ylide from 6a (*n* = 2); as well as amino/amido ylides from 7 and 8 with *n* = 2.

Although a neighboring amino group can exert an effect, E selectivity is attenuated relative to oxido and carboxy groups. The special role of anionic groups is illustrated by the reaction of 8CHO with amino or amido ylides from 9 (cf. entries 26 and 27). Also, the hydroxy ylide 11⁵ from 2,2,2-triphenyloxaphospholane⁵ (10) reacted with 8CHO to give a 73:27 Z/E mixture of



homocinnamyl alcohols (entry 4), whereas the corresponding γ -oxido ylide **2** furnished an ca. 4:96 $\underline{Z}/\underline{E}$ mixture (entries 3, 5, 6).

To explore the "trans-selective Wittig" mechanism, we experimented with three α -deuterated ylides: $\text{O}_3\text{P}=\text{CD}(\text{CH}_2)_2\text{CH}_3$ (**12**), $\text{O}_3\text{P}=\text{CD}(\text{CH}_2)_2\text{O}^-\text{Li}^+$ (**13**), and $\text{O}_3\text{P}=\text{CD}(\text{CH}_2)_3\text{COO}^-\text{Li}^+$ (**14**). As a model, ylide **12** was produced in THF from $\text{O}_3\text{P}^+\text{CD}_2(\text{CH}_2)_2\text{CH}_3 \text{Br}^-$ with *n*-butyllithium (1.6 M in hexane, 1.0 mol-equiv), reacted with OCHO at -78°C to form a Wittig intermediate, treated with 5 mol-equiv of hexamethyldisilazane (proton source), and rapidly warmed to 60°C to liberate olefin. The olefinic products ($\underline{Z}/\underline{E}$ = 62:38) contained ca. 85% deuterio species by GLC/MS (equal for each isomer), corresponding to a small amount (ca. 15%) of deuterium wash-out by H/D exchange. Using this procedure, ylide **13** was reacted with OCHO to give a mixture of homocinnamyl alcohols ($\underline{Z}/\underline{E}$ = 12:88), each containing ca. 70% D (GLC/MS). If \underline{E} alkene formation with **13** depended on a "trans-selective Wittig" mechanism, then a statistical distribution of exchangeable H and D (i.e., ca. 17% D) would have been realized in the homocinnamyl alcohols. An analogous experiment (-78°C) involving ylide **14** and OCHO yielded a mixture of 6-phenyl-5-hexenoic acids ($\underline{Z}/\underline{E}$ = 20:80), each containing ca. 75% D (GLC/MS).

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Table I. Wittig Reactions with Benzaldehyde and Lithium Bases

phosphonium salt	base (mol-equiv)	Z/E ratio	isolated yield	entry no. (remarks)
4a (n = 2)	LHMD (2.1)	28/72	14%	1 (0°C)
4a (n = 2)	nBuLi (2.1)	3/97	10	2 (ref 2a,2b)
4b (n = 3)	LHMD (2.1)	4/96	80	3
4b (n = 3)	* (1.0)	73/27	50	4 (*)
4b (n = 3)	LHMD (2.1)	6/94	83	5 (10 + LHMD)
4b (n = 3)	LHMD (2.1)	4/96	59	6 (ref 3a)
4c (n = 4)	LHMD (2.1)	15/85	--	7
4d (n = 5)	LHMD (2.1)	26/74	--	8
4e (n = 8)	LHMD (2.1)	59/41	50	9
4f (n = 11)	LHMD (2.1)	62/38	68	10
5a (n = 3)	LHMD (2.1)	10/90	--	11 (0°C)
5b (n = 4)	LHMD (2.1)	7/93	61	12
5c (n = 5)	LHMD (2.1)	13/87	74	13
5d (n = 7)	LHMD (2.1)	31/69	48	14
5e (n = 8)	LHMD (2.1)	63/37	28	15
5f (n = 11)	LHMD (2.1)	60/40	--	16
6a (n = 2)	LHMD (1.1)	31/69	70	17
6b (n = 3)	LHMD (1.1)	44/56	47	18
6c (n = 4)	LHMD (1.1)	47/53	--	19
6d (n = 6)	LHMD (1.1)	52/48	--	20
7	LHMD (1.1)	26/74	--	21
7	nBuLi (1.0)	19/81	45	22
7	LHMD (2.1)	17/83	--	23
7	nBuLi (2.1)	11/89	37	24
8	nBuLi (2.1)	18/82	22	25
9	nBuLi (1.0)	27/73	--	26
9	nBuLi (2.1)	13/87	--	27
3	LHMD (1.1)	50/50	86	28
3	LHMD (1.1)	55/45	60	29 (1 RCOO ⁻ Li ⁺)
3	LHMD (1.1)	63/37	--	30 (5 RCOO ⁻ Li ⁺)
3	LHMD (1.1)	63/37	87	31 (1 RO ⁻ Li ⁺)
3	LHMD (1.1)	53/47	--	32 (5 RO ⁻ Li ⁺)

* 10 was generated from 4b with NaH, isolated, and heated with ϕ CHO.