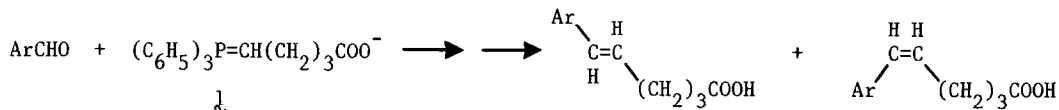


TRANS STEREOSELECTIVITY IN THE REACTION OF
 (4-CARBOXYBUTYLIDENE)TRIPHENYLPHOSPHORANE WITH AROMATIC ALDEHYDES

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Abstract: Aromatic aldehydes react with λ to give predominantly trans 6-aryl-5-hexenoic acids, under special conditions. A systematic study of the reaction of λ with aldehydes, in a preliminary attempt to define the cause and scope of the trans stereoselectivity, is reported.

The Wittig reaction can be an effective method for stereoselective synthesis of carbon-carbon double bonds.¹ Aldehydes react with lithium-salt-free, non-stabilized (or "reactive") phosphonium ylides to produce predominantly cis olefins, and with stabilized ylides to produce predominantly trans olefins.¹ Generally, non-stabilized ylides will not afford high trans stereoselectivity directly in their reaction with aldehydes, even in the midst of lithium salts and non-polar solvents.¹ However, the procedure of Schlosser can circumvent this problem indirectly via equilibration of intermediate "betaines" with the strong base, phenyllithium.² We report here a Wittig reaction, entailing the condensation of non-stabilized ylide λ with aromatic aldehydes, which displays unprecedentedly high trans stereoselectivity. The unusual stereocontrol appears to be induced by the polar, carboxylate end-group.



Reaction of benzaldehyde with λ , generated from $(\text{C}_6\text{H}_5)_3\text{P}^+(\text{CH}_2)_4\text{COOH Br}^-$ (λ) and dimsyl sodium (DMSO-Na) in dimethylsulfoxide (DMSO), conditions that are widely employed for Wittig reactions with λ ,³ provided a good yield of 6-phenyl-5-hexenoic acid⁴ with a 50/50 cis/trans ratio.⁵ Seeking to improve the volume efficiency and work-up of this reaction, we explored alternative solvents and bases, whereupon we discovered that a surprisingly strong bias toward trans isomer (87%) could be achieved with lithium hexamethyldisilazide (LiNSi_2) in tetrahydrofuran (THF) (Table, entry 2). Under the same lithium-"silazide" conditions, reaction of benzaldehyde with $(\text{C}_6\text{H}_5)_3\text{P}=\text{CHCH}_3$ (λ) gave β -methylstyrene with a 43/57 cis/trans ratio (Table, entry 11); the same (43/57) ratio was also obtained with one mol-equiv of lithium acetate present. Thus, the trans stereoselectivity for λ may be associated with an intramolecular interaction involving the carboxy terminal group. This idea was further substantiated by analogous shifts of stereoselectivity under diverse conditions: NaNSi_2 (λ vs. λ : 35/65 vs. 76/24), KNSi_2 (λ vs. λ : 39/61 vs. 77/23), KOtBu (λ vs. λ : 40/60 vs. 80/20), and DMSO-Na (λ vs. λ : 50/50 vs. 85/15) (Table, entries

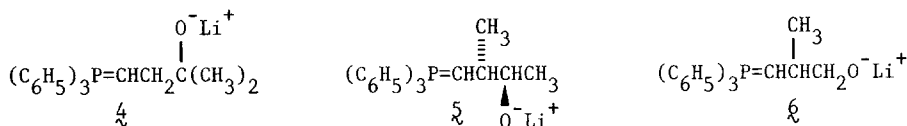
7 vs. 12; 8 vs. 13; 9 vs. 14; 1 vs. 10).

The effects of solvent, coordinating additives, and temperature on the reaction of $\mathbf{4}$ and benzaldehyde, under lithium-silazide conditions, were examined (Table). Ether (or ether/hexane, 1/1) enhanced the trans stereoselectivity (cis/trans = 8/92), but at the expense of yield (<10%). Lithium-selective macrocyclic polyether, 12-crown-4, reduced the trans stereoselectivity from 13/87 in the $\text{LiNSi}_2/\text{THF}$ reaction to 20/80 (entry 5), whereas 15-crown-5 and 18-crown-6 had little effect. Addition of hexamethylphosphoramide (HMPA, 10% by volume) caused a large decrease in trans stereoselectivity (cis/trans = 29/71), as expected (entry 6).^{1b} At a much lower temperature, -78°C, diminished trans stereoselectivity (cis/trans = 23/77) was observed (entry 3); at a higher temperature, ca. 120°C, stereoselectivity was slightly increased (cis/trans = 10/90).⁶

Interestingly, aliphatic aldehydes did not exhibit the phenomenon of trans stereoselectivity (entries 15-18). Reaction of nonanal with $\mathbf{4}$ using LiNSi_2 in THF gave 5-tetradecenoic acid with a cis/trans ratio of 73/27 (entry 16), which is close to the ca. 70/30 ratio expected for a non-stabilized ylide, devoid of a polar end-group, under standard lithium-salt/THF conditions (also see entry 17).^{7,8} Lithium-salt-free, dipolar-solvent conditions afforded the expected cis stereoselectivity (cis/trans = 89/11) (entry 15).^{1b,9}

With substituted aromatic aldehydes under $\text{LiNSi}_2/\text{THF}$ conditions (entries 19-22), electron-withdrawing groups (CN, NO_2 , Cl) furnished less trans isomer, whereas an electron-releasing group (OCH_3) furnished more.¹⁰ Notably, the reaction of p-anisaldehyde with $\mathbf{4}$ gave 6-(p-methoxyphenyl)-5-hexenoic acid in 92% isolated yield with 94% trans isomer content (entry 19). Furfural showed less trans stereoselectivity relative to benzaldehyde (entry 23).

The effect of anionic residues, such as the carboxylate group in our work, on the stereochemistry of the Wittig reaction has received scant attention. Salmond, et al., reported that alkoxide-ylide $\mathbf{4}$ reacts with aliphatic aldehydes to give trans-enriched homoallylic alcohols (cis/trans = ca. 15/85).¹¹ Trans stereoselectivity in the reaction of $\mathbf{5}$ with benzaldehyde (cis/trans = 15/85),¹² and $\mathbf{6}$ with indole-4-carboxaldehyde,¹³ was recently noted by Kozikowski, et al. The influence of the alkoxide group was attributed to an intrinsic Schlosser-type, trans-stereoselective Wittig mechanism, wherein deprotonation/equilibration of the intermediate "betaine" is effected by the basic alkoxide (an explanation which remains to be tested).¹⁴ A Schlosser rationalization is not applicable to our study because the carboxylate group is insufficiently basic to promote equilibration, a point which is supported by the experiment with $\mathbf{3}$ and added



lithium acetate. Thus, the trans stereoselectivity with $\mathbf{4}$ is induced by intramolecular participation of a nucleophilic group, which is remote from the ylide center. This may occur kinetically, via polar interactions in the transition state for carbon-carbon bond formation leading to "betaine" or oxaphosphetane intermediate, or thermodynamically, via polar effects during reversible dissociation of intermediate to reactants competitive with alkene formation.^{1,7,15,16} The difference between aromatic and aliphatic aldehydes may suggest that an intermediate-dissociation

Table^a

Entry	Aldehyde	Ylide	Base	Solvent	Cis/Trans	Yield %
1	C ₆ H ₅ CHO	λ	DMSO-Na	DMSO	50/50	83 ^b
2	C ₆ H ₅ CHO	λ	LiNSi ₂	THF	13/87	74 ^b
3 ^c	C ₆ H ₅ CHO	λ	LiNSi ₂	THF	23/77	
4	C ₆ H ₅ CHO	λ	LiNSi ₂	Et ₂ O	8/92	<10
5	C ₆ H ₅ CHO	λ	LiNSi ₂	THF ^d	20/80	
6	C ₆ H ₅ CHO	λ	LiNSi ₂	THF/HMPA	29/71	
7	C ₆ H ₅ CHO	λ	NaNSi ₂	THF	35/65	
8	C ₆ H ₅ CHO	λ	KNSi ₂	THF	39/61	
9	C ₆ H ₅ CHO	λ	KOtBu	THF	40/60 ^e	
10	C ₆ H ₅ CHO	ζ	DMSO-Na	DMSO	88/12	
11	C ₆ H ₅ CHO	ζ	LiNSi ₂	THF	43/57	60
12	C ₆ H ₅ CHO	ζ	NaNSi ₂	THF	76/24	
13	C ₆ H ₅ CHO	ζ	KNSi ₂	THF	77/23	
14	C ₆ H ₅ CHO	ζ	KOtBu	THF	80/20	
15	nonanal	λ	DMSO-Na	DMSO	89/11	
16	nonanal	λ	LiNSi ₂	THF	73/27	
17	nonanal	ζ	LiNSi ₂	THF	79/21	
18	(CH ₃) ₂ CHCHO	λ	LiNSi ₂	THF	79/21	
19	pMeOC ₆ H ₄ CHO	λ	LiNSi ₂	THF	6/94	92 ^b
20	pCNC ₆ H ₄ CHO	λ	LiNSi ₂	THF	35/65	78 ^b
21	mClC ₆ H ₄ CHO	λ	LiNSi ₂	THF	21/79	75 ^b
22	pNO ₂ C ₆ H ₄ CHO	λ	LiNSi ₂	THF	41/59	<10
23	furfural	λ	LiNSi ₂	THF	38/62	88 ^b

(a) Reactions were conducted at 25°C (except entry 3). All products were analyzed by ¹H NMR and, as methyl esters, by GLC and GLC/mass spec. Isomer ratios are GLC values. ¹³C NMR was used to confirm the nonanal reaction products. All yields are for isolation. (b) Isolated and purified by distillation. (c) At -78°C. (d) Containing 1 mol-equivalent of 12-crown-4. (e) Sensitive to reaction conditions; results varied from 15/85 to 50/50, but ca. 40/60 was generally obtained.

mechanism (excluded for aliphatic but not aromatic aldehydes^{1a,15b}) is critical for the carboxylate-induced trans stereoselectivity.

Further work is required to understand the underlying causes of nucleophilic-group-induced trans stereoselectivity in the Wittig reaction.¹⁷ We are currently investigating carboxylate and alkoxide ylides with varied chain lengths between the end-group and ylide center.

Preparative Experimental Procedure¹⁹ -- Powdered ζ (8.84 g, 20 mmol) in dry THF (30 ml), under N₂, was treated with lithium hexamethyldisilazide (7.03 g, 42 mmol, Petrarch) in THF (20 ml) at 25° with stirring. After 15 min, benzaldehyde (2.12 g, 20 mmol) in THF (10 ml) was added at 25°, rapidly decolorizing the red-orange mixture. After 15 min, water (50 ml) and

ether (50 ml) were added. The organic phase was rinsed with water (20 ml). The combined aqueous solution was washed (EtOAc, 50 ml), acidified (10% HCl), and extracted with EtOAc (2 x 50 ml). The united EtOAc extracts were rinsed (H₂O), dried, and concentrated. Kugelrohr distillation gave 2.80 g (74%) of pure 6-phenyl-5-hexenoic acid, containing 87% trans isomer.

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2. M. Schlosser and K. F. Christmann, Angew. Chem. Intl. Edit., **5**, 126 (1966).
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4. A sample of trans-6-phenyl-5-hexenoic acid, from an independent synthesis [J. Cousseau and M. Lamant, Bull. Soc. Chim. Fr., 4702 (1967)], was kindly afforded to us by Dr. Michael Wachter (Ortho Pharmaceutical Corp.).
5. The 50% trans isomer in this reaction is much greater than expected given the 85/15 cis/trans ratio in the dimethyl-sodium reaction of benzaldehyde and λ (Table, entry 10), reflecting the influence of the carboxylate group on the Wittig stereochemistry (vide infra).
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19. In modifications of this procedure we found that (1) LDA gives results similar to LiNSi₂; (2) the LiNSi₂ and benzaldehyde may be added neat, with cooling; (3) 1.5 equiv of LiH may be substituted for 1 equiv of LiNSi₂ for the initial neutralization of the carboxylic acid.

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