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HORNER-WITTIG REACTIONS USING DIBENZOPHOSPHOLE OXIDES: STEREOCHEMICALLY CONTROLLED REDUCTION OF KETONES

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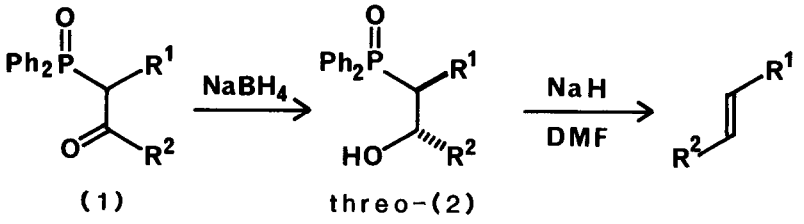
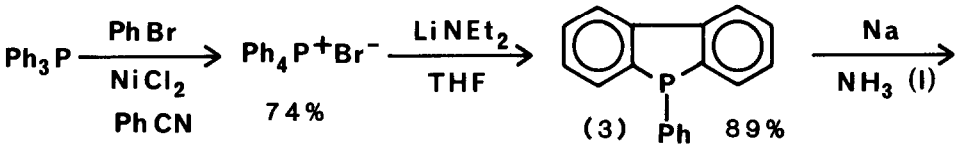
Reduction of ketones having an α-dibenzophosphole-5-oxide group with $NaBH_4$, L-Selectride, or Superhydride gives threo Horner-Wittig intermediates and hence E-alkenes, while $NaBH_4/CeCl_3$ gives erythro intermediates and hence Z-alkenes.

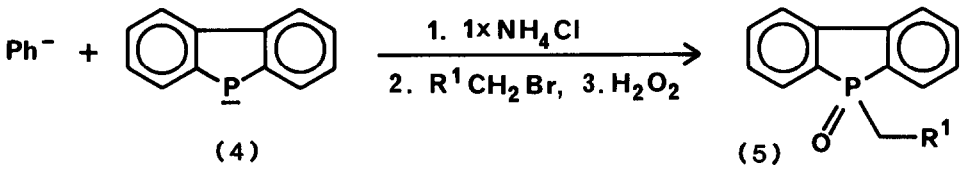
The Horner-Wittig reaction with the diphenylphosphinoyl (Ph_2PO) group is erythro selective[1] while reduction of the α-Ph_2PO-ketones (1) with $NaBH_4$ gives threo intermediates (2) stereoselectively[2] and hence E-alkenes[3] by stereospecific[4] elimination of $Ph_2PO_2^-$. Reduction of the ketones (1) often gives higher stereoselectivity than the Horner-Wittig reaction itself making an erythro selective reduction desirable. The elimination also sometimes causes problems[5] and we report that our attempt to improve this final step by using the more electrophilic dibenzophosphole oxide[6] has revealed that reduction of the ketones (6) shows remarkable stereochemical control not shown by the ketones (1).



(1) threo-(2)



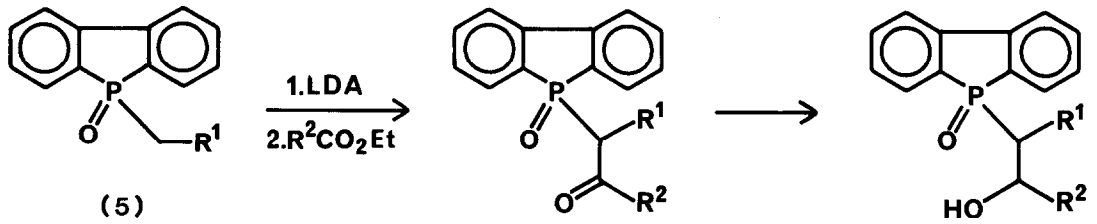
(3)



(4) (5)

The phosphine oxides (5) were prepared from Ph_3P via reductive cleavage of phosphole[6,7] (3) and capture of the very nucleophilic anion (4) with alkyl halides followed by oxidation with H_2O_2. The methods usually used[1] for Ph_2PO compounds, such as the hydrolysis of phosphonium salts or the attack of

Grignard reagents on Ph_2POCl, are not suitable for dibenzophospholes as opening of the five-membered ring occurs. Acylation[8] of the anion of (5) (using LDA not BuLi, which acts as a nucleophile on P, giving reduced yields and several by-products) with esters or lactones gave good yields of the ketones (6) (table 1).



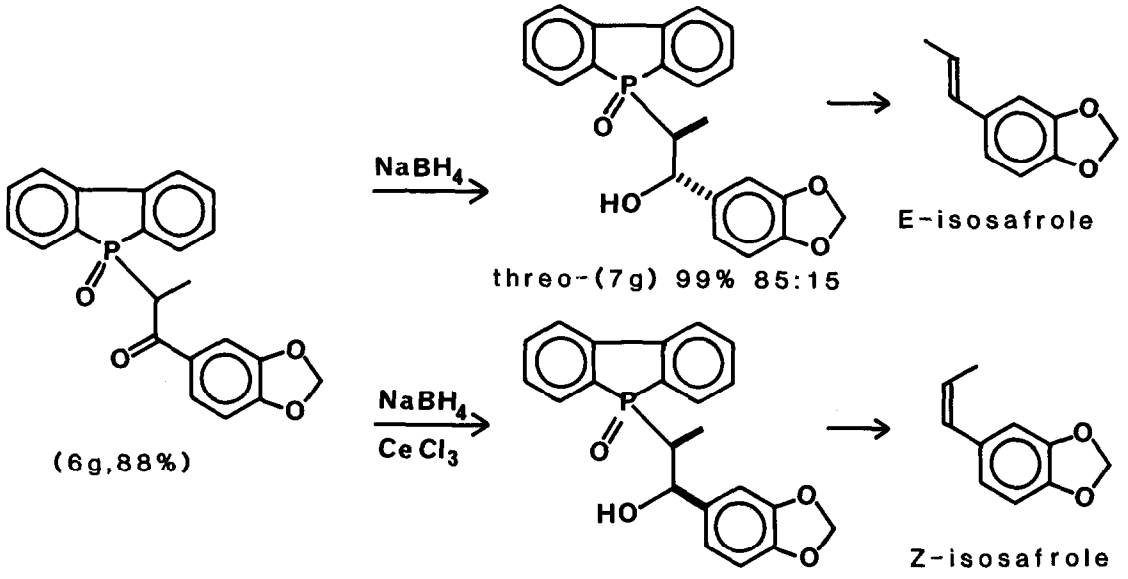
The standard reducing agent ($NaBH_4$, MeOH, 0 °C, 2 h) for the α-Ph_2PO-ketones (1) gave similar results with the phospholes (6) (table 1), >85% threo-alcohol (7) being formed except for (6c) where the OH group evidently interferes. Addition of $CeCl_3$ (using the Danishefsky variation of the Luche[9] reagent: $NaBH_4$, $CeCl_3$, MeOH, -78 °C) reverses the selectivity to favour the erythro isomer (table 1) though not usually with such high stereoselectivity.

Table 1: Stereoselectivity in Reduction of Ketones (1) and (6)

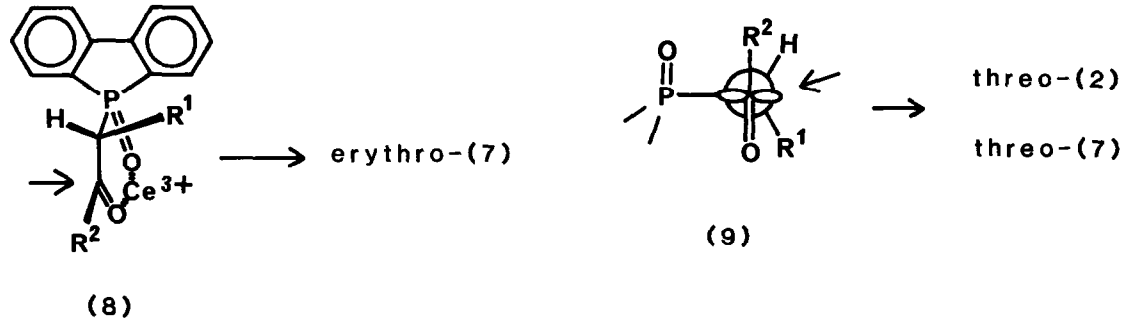
			Synthesis and Reduction of Ketones (6)					Reduction of Ketones (1)		
			Yield[a]	$NaBH_4$		$NaBH_4/CeCl_3$		$NaBH_4$		
Series	R^1	R^2	(6)	Yield	Ratio[b]	Yield	Ratio[b]	Yield	Ratio[b]	Ref
a	Me	Ph	99%	86%	88:12	97%	16:84	88%	88:12	1
b	Me	$(CH_2)_2OH$	38%	97%	85:15	97%	12:88	100%	70:30	10
c	Me	$(CH_2)_3OH$	91%	93%	78:22	87%	12:88	76%	74:26	10
d	Me	$(CH_2)_3OR$[c]	90%[c]	72%	75:25	57%[d]	14:86	63%	70:30	10
e	Me	2-furyl	92%	94%	95:5	92%	35:65	-	-	
f	Me	2-pyridyl	94%	91%	90:10	92%	75:25	-	-	
g	Me	e	88%	99%	85:15	99%	15:85	96%	94:6	1
h	Et	Ph	71%	99%	93:7	98%	14:86	99%	93:7	
i	Et	Me	62%	94%	86:14	99%	29:71	-	-	
j	Et	$(CH_2)_5OH$	62%	89%	89:11	90%	18:82	81%	85:15	11
k	Et	C_6H_{11}[f]	72%	reduction very slow				-	-	
l	$(CH_2)_2OH$	Ph	76%[g]	100%	97:3	100%	59:41	92%	95:5	11

a. from (5), LDA, and ester or lactone unless otherwise stated.
b. threo:erythro
c. R = t-$BuPh_2Si$, from (7c) by silylation.
d. and 12% silanol: desilylation occurs during reduction.
e. R^2= 3,4-methylenedioxyphenyl, for (7g) see diagrams.
f. cyclohexyl.
g. by acyl transfer, see reference 11.

This reversal is not found with the α-Ph_2PO-ketones (1), instead a lower threo selectivity is observed; e.g. (1h) gives 93:7 threo:erythro (2h) with $NaBH_4$ and 77:23 with $CeCl_3$. These methods allow the isolation of pure erythro or threo intermediates (7) in high yield from the same starting material and can thus be used to prepare pure E- or Z-alkenes.[6] The synthesis of both intermediates threo-(7g) and erythro-(7g) for the Horner-Wittig synthesis[1] of isosafrole illustrates this approach.



The only steric difference between the dibenzophosphole oxide and Ph_2PO groups is the rigidity of the former. This may allow the chelated ketone (8) to form since the planar rings are held away from R^1, whereas a similar structure with Ph_2PO would have at least one Ph group close to R^1. Reduction of (8) from the opposite side to R^1 now gives erythro-(7). The effect is reduced (6e) or disappears (6f, l) when an alternative chelating group is provided. In the absence of cerium, we prefer the Felkin model (9) for both reductions and suggest that, for the α-Ph_2PO-ketones (1), cerium decreases the stereoselectivity by a small amount of chelation.



Another chelating agent, $Zn(BH_4)_2$, has a similar effect, while other non-chelating agents with greater bulk: Superhydride[12] (Et_3BHLi) or L-Selectride[12] ($s\text{-}Bu_3BHLi$) give even greater threo selectivity (table 2) with (6a). However, L-selectride reductions were very slow and starting material was recovered.

Table 2: Effects of other Reducing Agents.

Compound	Reagent	Conditions	Yield	Threo:Erythro
(6a)	$NaBH_4$	MeOH, 0°C, 2 h	86%	88:12
(6a)	$NaBH_4/CeCl_3$	MeOH,-78°C, 1 h	97%	16:84
(6a)	$Zn(BH_4)_2$	Et_2O,-78°C, 15 h	95%	<2:98
(6a)	$s\text{-}Bu_3BHK$	THF,-78°C, 16 h	82%	91:9
(6a)	$s\text{-}Bu_3BHLi$	THF, 0°C, 5 h	90%	98:2
(6a)	Et_3BHLi	THF,-78°C, 4 h	92%	96:4
(6g)	Et_3BHLi	THF,-78°C, 6 h	90%	98:2

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12. Trade names, compounds supplied by the Aldrich Chemical Company.

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