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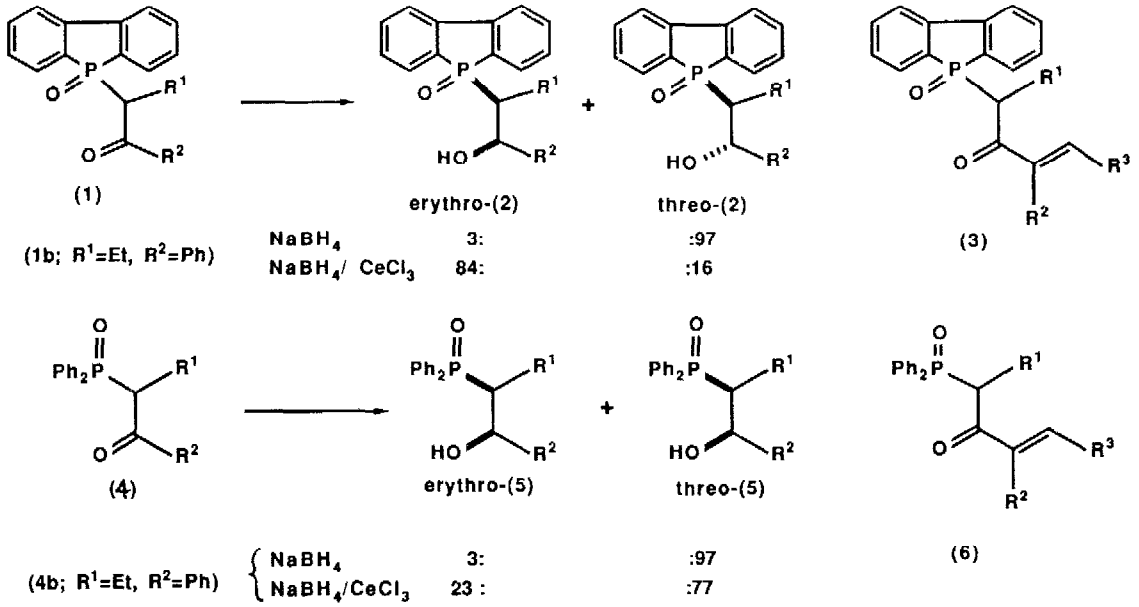
REVERSED STEREOCHEMICAL CONTROL IN THE REGIOSELECTIVE REDUCTION OF HINDERED DIPHENYLPHOSPHINOYL (Ph_2PO-) KETONES AND ENONES

Jason Elliott, David Hall, and Stuart Warren*
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

Reduction of α'-diphenylphosphinoyl enones (**6**) and crowded α-diphenylphosphinoyl ketones (**4**) with sodium borohydride in the presence of cerium chloride gives the otherwise difficult to obtain erythro-alcohols (**5**) and (**7**).

The regioselective 1,2 reduction of conjugated enones is now readily accomplished using the Luche[1] conditions ($NaBH_4$, $CeCl_3$, MeOH, -78 °C). We have shown[2] that these conditions also lead to the stereo-selective reduction of the ketones (**1**) and enones (**3**) giving erythro alcohols (**2**) and hence Z-alkenes[3] in good yield in contrast to the normally threo-selective reduction of both (**1**) and the α-Ph_2PO ketones (**4**) with $NaBH_4$ alone. We said that this reversal of stereoselectivity in the presence of cerium did not occur with the Ph_2PO compounds which gave poorer threo selectivity, e.g. (**4b**), in most cases. We now report that a wider examination of substituted ketones (**4**) and enones (**6**) reveals that this conclusion (and inevitably its explanation) is wrong and that cerium-catalysed reduction of ketones (**4**) and (**6**) can in fact be used in many cases to prepare the erythro alcohols (**5**) and (**7**) in high yield.



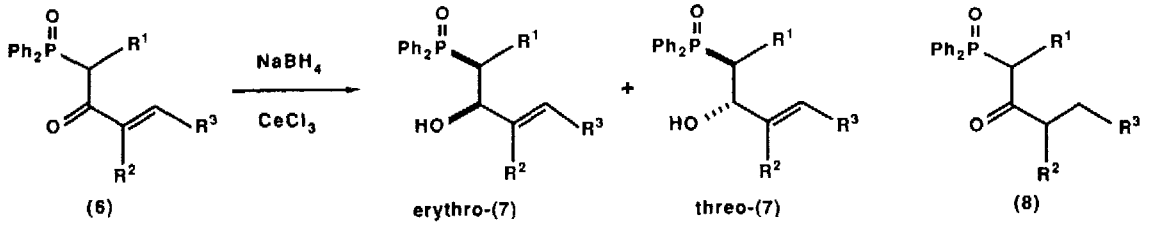
Work on α'-Ph_2PO enones led us to study their reduction under the Luche conditions.[1] Two series of molecules were investigated: those with achiral R^1 (**6**) prepared by standard methods,[4] and pairs of diastereoisomers (**9**) and (**11**) separated by h.p.l.c. The stereochemistry of (**9e**) was determined by X-ray crystallography.[5] Reduction with $NaBH_4$ alone gave 1,4-reduction to the saturated ketones (**8**), but $NaBH_4/CeCl_3$ gave totally regioselective 1,2-reduction accompanied by a remarkably high stereoselectivity. The results summarised in the table led us to examine also a variety of simple ketones (**4**) and the following conclusions can be drawn:

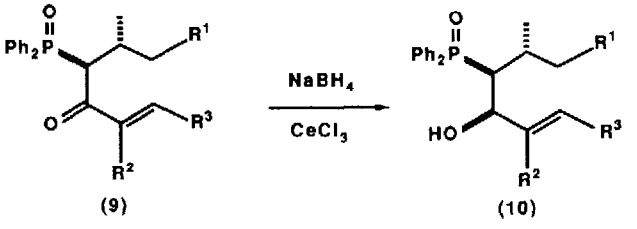
(a) With R^1=Me or n-alkyl, ketones (**4a,b**) and enones (**6a-f**) are reduced by $NaBH_4/CeCl_3$ to give the weak threo selectivity observed before.[2]

(b) If R^1 is branched β' to the carbonyl group, reduction of both ketones (**4d,e**) and enones (**6h**) becomes highly stereoselective in the reverse sense, and the erythro alcohols (**5**) and (**7**) may be isolated in high yield.

(c) If R^1 gets too large (**6i**), some 1,4-reduction of the enones to give the saturated ketone (**8**) may occur, though the 1,2-reduction is still highly stereoselective [as is the reduction of the ketones (**4e**)].

(d) If there is a second chiral centre β' to the carbonyl group, both diastereoisomers (**9**) and (**11**) give the same high erythro selectivity. There is essentially no match or mis-match,[6] the stereoselectivity being dominated by the α' chiral centre (bearing Ph_2PO).





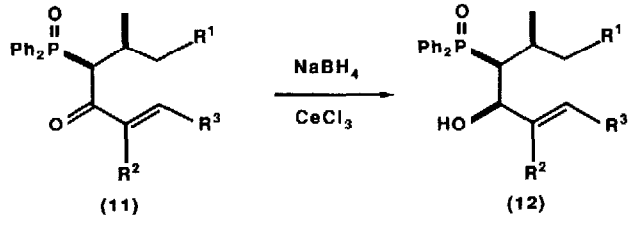


Table. Reduction of α-Ph_2PO Ketones and α'-Ph_2PO Enones with $NaBH_4/CeCl_3$*

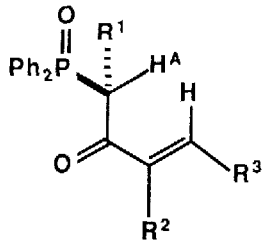
Starting Materials				Product	Yield	Erythro
	R^1	R^2	R^3		(%)	:Threo
(1a)	Me	Ph	-	(2a)	97	86:14[a]
(4a)	Me	Ph	-	(5a)	90	30:70
(1b)	Et	Ph	-	(2b)	98	84:16[a]
(4b)	Et	Ph	-	(5b)	100	23:77[a]
(4c)	CH_2CH_2OH	$(CH_2)_2CO_2Me$	-	(5c)	77	<5:95[a,b]
(4d)	i-Pr	Ph	-	(5d)	100	>95:5[c]
(4e)	C_6H_{11}[d]	Ph	-	(5e)	95	>95:5[c]
(6a)	Me	Me	H	(7a)	95	38:62
(6b)	Me	H	Me	(7b)	92	45:55
(3c)	Me	H	n-Pr	(2c)	83	93:7
(6c)	Me	H	n-Pr	(7c)	71	50:50
(6d)	Me	Me	Me	(7d)	90	25:75
(6e)	Me	i-Pr	H	(7e)	91	22:78
(6f)	n-Bu	Me	Me	(7f)	85	55:45
(6g)	$i\text{-}PrCH_2$	Me	Me	(7g)	90	67:33
(6h)	i-Pr	Me	Me	(7h)	93	>95:5[c]
(6i)	C_6H_{11}[d]	Me	Me	(7i)	48[e]	>95:5[c]
(9a)	Me	Me	H	(10a)	90	>95:5[c]
(9b)	Me	Me	Me	(10b)	79	>95:5[c]
(11b)	Me	Me	Me	(12b)	90	>95:5[c]
(9c)	Me	Et	H	(10c)	89	>95:5[c]
(11c)	Me	Et	H	(12c)	92	>95:5[c]
(9d)	$OCPh_3$	Me	H	(10d)	88	>95:5[c]
(9e)	$OCPh_3$	Me	Me	(10e)	71	>95:5[c]
(11e)	$OCPh_3$	Me	Me	(12e)	88	>95:5[c]

*All reductions were carried out by adding $NaBH_4$ (30 mmol) slowly to a solution of the enone (10 mmol) and $CeCl_3$ (10 mmol) in EtOH (10 mls) at -78 °C. After 30 mins, water and dil. HCl were added. Extraction with CH_2Cl_2, drying, and evaporation gave the alcohol.

[a]See ref. 2. [b]Erythro could not be detected, yield is of pure threo. [c]Threo could not be detected, yield is of pure erythro. [d]Cyclohexyl. [e]And 43% of the saturated ketone (**8i**).

We have n.O.e., i.r., and X-ray evidence that the enones prefer conformation (**13**) with H^A in the plane of the s-trans enone.[5] ^1H N.m.r. experiments under the reaction conditions show that the cerium atom is close to the methyl group and the ortho aromatic protons in (**9**) and (**11**) and suggest that Ce^{3+} is chelated by C=O and P=O [and OH in (**4c**)]. We suggest that the normal threo selectivity arises from conformation (**14**) [enhanced by OH chelation in (**4c**)], the reduced threo selectivity (R^1 small) from attack on either side of confor-

mation (15), and the reversed erythro selectivity from attack opposite the large R^1 group in conformation (15). Transition state (14) corresponds to the Felkin[3] model, while (15) is distorted by chelation and steric repulsion between the large R^1 group and the co-ordination sphere of cerium.



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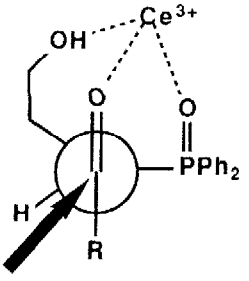

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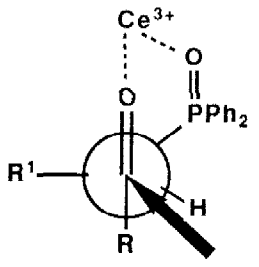

(15)

The stereospecific formation of E alkenes from threo alcohols (5) and Z alkenes from erythro alcohols (5) is well established.[3] Threo alcohols (5) of most types are available[3,7] by $NaBH_4$ reduction of substituted ketones (4), but erythro alcohols (5) with branched R^1 and allylic alcohols (7), (10), and (12) were available only by the Horner-Wittig reaction[3,8] which shows poor stereoselectivity in these cases. The cerium-catalysed reductions now make available a wide range of erythro alcohols with previously unattainable stereoselectivity. Both stereoisomers of the allylic alcohols (7) can be used in stereochemically controlled allylic transpositions.[8]

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References and Notes

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