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The Stereoselective Horner-Wittig Reaction with Phosphine Oxides: Synthesis of Hindered *Z* Alkenes via Luche Reduction

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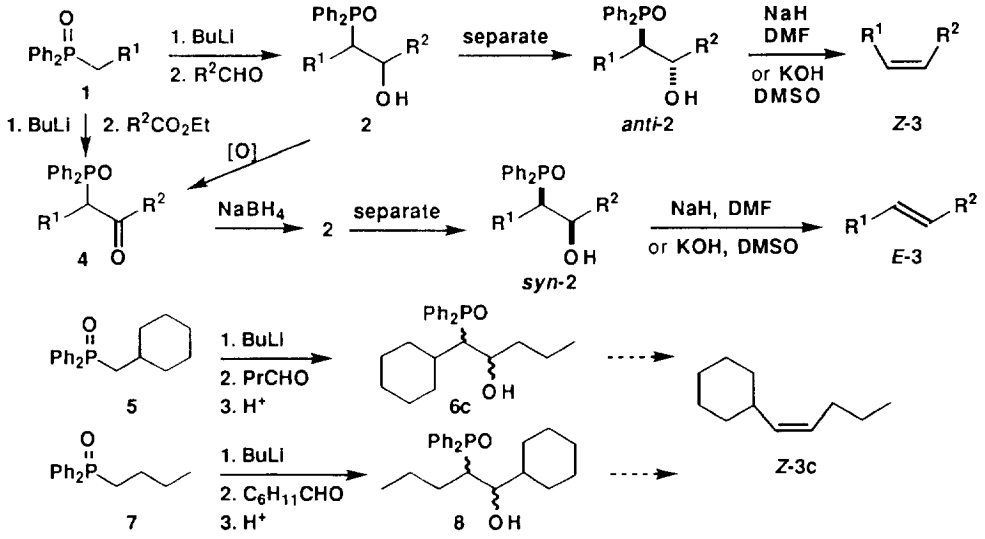
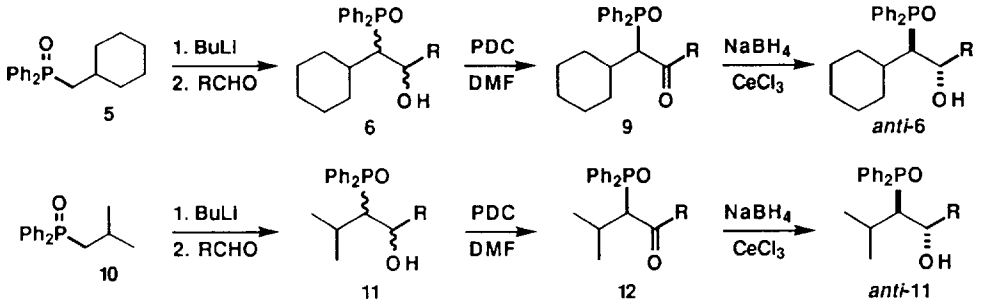
Abstract: The natural *anti* selectivity of the Horner-Wittig reaction with phosphine oxides is reduced when there is a branched chain next to the new C=C double bond. A better approach is Luche reduction of the corresponding ketones which gives high *anti* selectivity when the branched chain is placed on the side chain next to the phosphine oxide.

We have described[1] a version of the Horner-Wittig reaction in which a lithium derivative of a phosphine oxide reacts with an aldehyde to give predominantly *anti* alcohols **2** and hence, after separation and stereospecific elimination with a sodium or potassium base, pure *Z* alkene *Z*-**3**. The corresponding *E* alkene is formed by stereoselective reduction ($NaBH_4$) of the ketone **4**. These reactions have been used to make a large number of substituted alkenes with a wide variety of structural types and functional groups.[1] Others have used these methods to make FK-506[2] and the oudemansins[3] A and B.



One serious limitation remains: the *E* selective route is successful when there is a branched chain next to the alkene, but the *Z* selective route is not. Typically, neither **6c** nor **8** is a suitable precursor for the simple *Z* alkene *Z*-**3c** (see later for a good route to *Z*-**3c**). The reaction of the lithium derivative of **5** with butanal gave a 53:47 mixture of *syn*:*anti* **6c**, while reaction of the lithium derivative of **7** with cyclohexane carboxaldehyde gave a 50:50 mixture of *syn*:*anti* **8** which could not be separated by chromatography. We now report that Luche[4] reduction of the ketones with the branch on the phosphine oxide side chain (R^1 in **4**) using $NaBH_4$ and $CeCl_3$ at –78 °C is very stereoselective in favour of *anti*-**2** giving high yields of *anti*-**6** and

11. We had previously reported[5] a few examples of this reversal of stereoselectivity, mainly with enones, and we had established a similar reversal of stereoselectivity in the presence of Ce(III) in the dibenzophosphole series,[5] but we now report that it is a general route to branched *Z*-alkenes and that it is not affected by potentially chelating groups on the phosphorus atom or on the ketone side chain (R^2 in **4**).



We have studied two series of compounds derived from the phosphine oxides **5** (**1**; R^1 = cyclohexyl, table 1) and **10** (**1**; R^1 = i-propyl, table 2). Lithiation (BuLi) and reaction with a series of aldehydes gave mixtures of diastereoisomers of **6** and **11** in good yield (tables). The *syn:anti* ratio was measured by NMR and then the mixture was oxidised to the ketones **9** and **12** with bleach in acetic acid,[6] PDC in dry DMF,[7] or the Dess-Martin periodinane.[8] Reduction of these two series of ketones with $NaBH_4$ in EtOH and with the Luche reagent ($NaBH_4/CeCl_3$) in EtOH at –78 °C gave alcohols **6** and **11** in the ratios shown in the tables.

Table 1: Stereoselective Luche Reduction of the α-Diphenylphosphinoyl Ketones **9**.

		Yield	Ratio	Yield	$NaBH_4$ Reduction		Luche Reduction	
Entry	R	(%) **6**	*anti:syn*	(%) **9**	Yield (%)	*anti:syn*	Yield (%)	*anti:syn*
1	Me	**6a**, a	50:50	**9a**, –	–	–	–	–
2	Et	**6b**, 91	46:54	**9b**, 84	93	40:60	81	>91:9
3	n-Pr	**6c**, 100	53:47	**9c**, 96	74	38:62	84	>96:4
4[b]	i-Pr	**6d**, 98	47:53	**9d**, 92	56	19:81	52	88:12
5	Ph	**6e**, 80	80:20	**9e**, 67	71	24:76	100	100:0
6	2-$MeOC_6H_4$	**6f**, 91	65:35	**9f**, 87	99	18:82	100	>96:4
7	4-$MeOC_6H_4$	**6g**, 99	75:25	**9g**, 63	–	–	–	–
8	2-furyl	**6h**, 72	75:25	**9h**, 68	100	20:80	98	97:3

[a]Not isolated, ref 1. [b]Compare this entry with entry 4 in table 2: the products would give the same alkene.

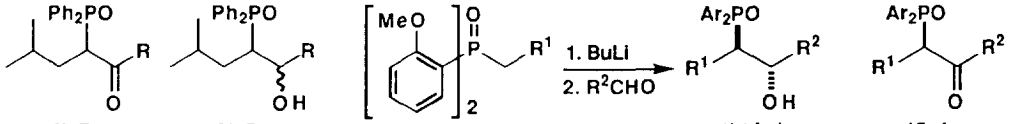
In every case the *anti* selectivity in the Luche reduction surpassed the *anti* selectivity in the Horner-Wittig reaction itself and in most cases surpassed even the selectivity in the best Horner-Wittig reactions.[1] From being the worst case, these branched chain compounds have become the best so that reduction of **9c** replaces the poor routes to *anti*-**6c** and *Z*-**3c** *via* **6c** or **8** described above. Stereoselectivity in the Horner-Wittig reaction depends on stereochemical preferences in a crowded transition state held rigid by the lithium atom. To get high selectivity it is best[1] to put the larger group as R^2 in **2**. The *syn* stereoselectivity in the $NaBH_4$ reduction of α-Ph_2PO-ketones is a Felkin-Anh selectivity and again gives better results when R^2 is large but R^1 is not.[1] Luche reduction of these ketones without a branch on the phosphine oxide side chain (R^1 in **4**) shows normal but reduced selectivity in favour of *syn*-**2**. Only when R^1 is branched as in **9** and **12**

is high *anti* selectivity found in the Luche reductions. Even moving the branch one further atom away from the Ph_2PO group removes the effect: ketone **4i** gives a 54:46 *anti:syn* ratio at 0 °C under the Luche conditions and 72:28 at –78 °C. Direct addition of **1**; R^1 = i-Bu to 4-$MeOC_6H_4CHO$ is a much better route as it gives only *anti*-**2i** isolated in 65% yield.

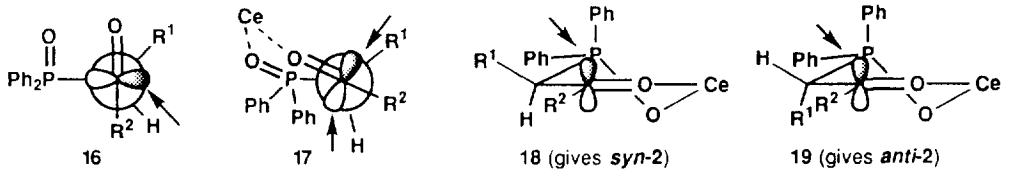
Table 2: Stereoselective Luche Reduction of the α-Diphenylphosphinoyl Ketones **12**.

		Yield	Ratio	Yield	$NaBH_4$ Reduction		Luche Reduction	
Entry	R	(%) **11**	*anti:syn*	(%) **12**	Yield (%)	*anti:syn*	Yield (%)	*anti:syn*
1	Me	**11a**, 85	42:58	**12a**, 71	87	35:65	83	77:23
2	Et	**11b**, 89	50:50	**12b**, 34	90	39:61	100	93:7
3	n-Pr	**11c**, 84	57:43	**12c**, 71	85	46:54	77	89:11
4[a]	C_6H_{11}	**11d**, 78	45:55	**12d**, 87	b		b	
5	Ph	**11e**, 79	67:33	**12e**, 69[c]	100	19:81	99	>94:6
6	2-$MeOC_6H_4$	**11f**, 93	64:36	**12f**, 88[d]	82	12:88	82	>99:1
7	4-$MeOC_6H_4$	**11g**, 87	68:32	**12g**, 82	100	28:72	100	97:3
8	2-furyl	**11h**, 83	70:30	**12h**, 75	96	17:83	96	>98:2

[a]Compare this entry with entry 4 in table 1: the products would give the same alkene. [b]No reaction. [c]Ref 1. [d]Oxidation with the Dess-Martin periodinane.[8]



We believe this high reversed stereoselectivity is the result of chelation of the ketone and phosphinoyl oxygen atoms by the Ce(III) atom.[6] We therefore examined whether other chelating groups could interfere with the selectivity. Entries 6 and 7 in table 2 show that selectivity with *ortho* and *para* OMe groups is about the same so chelation does not interfere there. The 2-furyl derivatives (entry 8) also give excellent and normal results. Kaufmann and Schwartze[9] have reported an enhanced *anti* selectivity in the Horner-Wittig reaction when the $(2\text{-}MeOC_6H_4)_2PO$ group replaces the Ph_2PO group in the Horner-Wittig step, e.g. **13**; R^1 = n-Pr gives >97:3 *anti:syn* selectivity with benzaldehyde. We therefore studied the reductions of the related ketones **15**; R^1=n-Pr, i-Pr; R^2=Ph by $NaBH_4$ alone or under the Luche conditions and found that, by contrast, results are virtually identical to those with the Ph_2PO group and extra chelation is again not involved.



The Felkin-Anh alignment[1] **16** is changed by chelation to something like **17** in which attack will still occur opposite the Ph_2PO group unless R^1 is branched. If the six-membered chelate is chair-like, an alternative explanation is that a small R^1 may choose an equatorial position **18**, but a branched R^1 will prefer an axial position away from the two phenyl groups **19**: axial attack then gives the observed stereoselectivity.

Similar explanations of other Ce-controlled stereoselective reductions have been advanced.[10] Attempts to extend this approach to more crowded alkenes were not successful: with an i-propyl group on one side and a cyclohexyl group on the other side of the double bond (tables 1 and 2, entry 4) reduction is difficult with **9d** and did not occur with **12d**. With a t-butyl group on either side, i.e. **4**; R^1 or R^2 = t-butyl, no reduction occurred with either $NaBH_4$ alone or $NaBH_4/CeCl_3$. Only with $LiAlH_4$ was there any reduction when R^2 = t-butyl but it gave a low yield and was *syn* stereoselective.

Elimination of $Ph_2PO_2^-$ with NaH/DMF or KOH/DMSO on the *anti* isomers is well established and usually stereospecific.[1,2] Examples include *anti*-**11e** to *Z*-**3e**; R^1 = i-Pr, R^2 = Ph in 78% yield with 0% *E* by g.l.c., *anti*-**11g** to *Z*-**3g**; R^1 = i-Pr, R^2 = 4-$MeOC_6H_4$ in 70% yield with 3% *E* by g.l.c. Examples where both R^1 and R^2 are alkyl are usually completely stereospecific.[11] Highest stereoselectivity for either *E* or *Z* alkenes is normally best achieved by putting the larger group next to carbonyl (R^2 in **2**) and not next to Ph_2PO. This work shows that excellent yields of *Z* alkenes with a branch next to the double bond are best achieved by reversing this preference: the branched group should be R^1 in **2**, i.e. in the phosphine oxide starting material.

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