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$TiCl_4$ Mediated $LiBH_4$ Reduction of β-Ketophosphine Oxides: a High Stereoselective Route to the Synthesis of *anti*-β-Hydroxyphosphine Oxides.

Giuseppe Bartoli*, Marcella Bosco and Letizia Sambri

Dipartimento di Chimica Organica "A.Mangini", v.le Risorgimento, 4, I-40136, Bologna, Italy

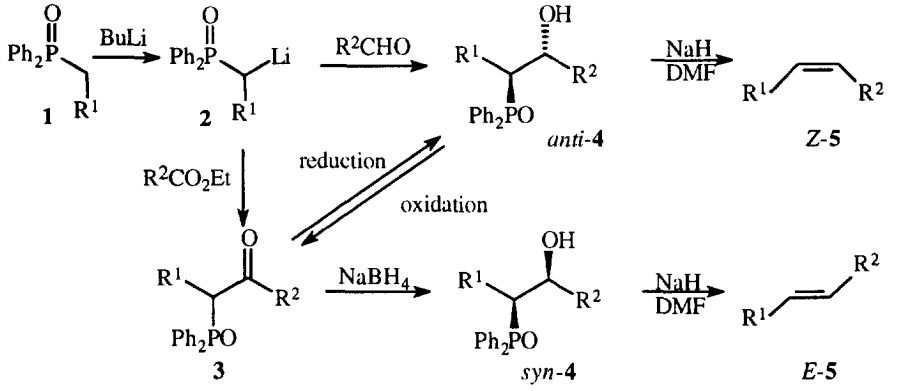
Enrico Marcantoni

Dipartimento di Scienze Chimiche, via S.Agostino 1, I-62032 Camerino (MC), Italy

Abstract: The reduction of an α-alkyl-β-ketophosphine oxide with $LiBH_4$ in presence of a strong chelating agent, such as $TiCl_4$, gives the corresponding β-hydroxyphosphine oxide in high yields and with high *anti*-diastereoselectivity independently from the size of both the α- and β-alkyl chains.

In the past years great attention has been devoted to the study of the Horner[1] reaction for the construction of stereodefined carbon-carbon double bond[2], since this methodology can offer some advantages over the more widely used Wittig and Wadsworth-Emmons approaches[3]. At variance with reactivity of phosphonium ylides and phosphonate carbanions, the condensation of a lithium alkylphosphine oxide (**2**) with an aldehyde is generally irreversible and leads to stable products with good *anti*-selectivity (*anti*-**4**), as shown in Scheme 1. *Anti*-**4** can be isolated as solid crystalline compounds and purified from the small amount of the *syn* isomer prior to submit them to stereospecific decomposition to *Z*-alkenes **5**.

Lithium alkylphosphine oxide derivatives show great synthetic flexibility. Starting from **1** it's possible to plan a synthesis of *E*-alkenes *via* a variant of the original Horner approach (called Warren variant)[4]: the reduction of β-ketophosphine oxide **3** (obtained from the reaction of **2** with an ester) with $NaBH_4$ in MeOH at 0 °C leads to *syn*-**4** which in turn stereospecifically give *E*-alkenes **5**.



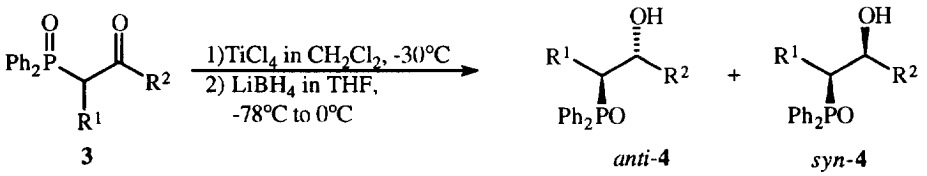
Scheme 1

Serious limitations remain: a very modest selectivity is observed when R^1 in **1** or R^2 in the aldeyde are α-branched alkyl chains[2]. In addition, in these cases the *Z* route is totally ruled out owing to the difficult in separation of the *syn* and *anti* isomers.

Recently Warren found[5] that the ketones **3** carrying in α-position a secondary alkyl substituent (R^1= ^{i}Pr or Chx) can be converted with high selectivity into hydroxy derivatives *anti*-**4** if the reduction process is carried out under Luche's conditions. However this methodology represents only a partial solution of the problem, since random selectivity is observed with linear α-alkyl substituents.

We report now a new general approach to *anti*-β-hydroxyphosphine oxides **4** based on the reduction of β-ketophosphine oxides **2** with $LiBH_4$[6] in THF at low temperature in the presence of a strong chelating agent as $TiCl_4$[7]. As shown in Table 1, the reduction of **3a-i** into *anti*-**4a-i**, under these conditions, proceeds with high yields and high selectivity, independently from the size of R^1 and R^2 (α-branched or linear substituents). In addition, our methodology shows a diastereoselectivity superior to previously reported procedures. For example compounds *anti*-**4a**, *anti*-**4b** and *anti*-**4i** were obtained from reaction of **2** with the appropriate aldehyde in 88/12, 79/21 and 53/47 *anti/syn* purity respectively[2]. The reduction of ketones **3a** and **3i** under Luche conditions gives *anti*-**4a** in 30/70 and *anti*-**4i** in 96/4 *anti/syn* ratio[2]. $TiCl_4$ mediated reduction of **3a**, **3b** and **3i** affords *anti*-**4a**, *anti*-**4b** and *anti*-**4i** respectively in 92/8, 98/2 and 97/3 *anti/syn* purity.

Table 1: Stereoselective reduction of β-Ketophosphine Oxides with $LiBH_4$-$TiCl_4$.



3 *anti*-**4** *syn*-**4**

entry	compound	R^1	R^2	product	yield%	*anti/syn* [a]	isolated *anti* (%)[b]
1	**3a**	Me	Ph	**4a**	98	90/10	81[b]
2	**3b**	Me	Chx	**4b**	97	98/2	88[b]
3	**3c**	n-Pr	Bu	**4c**	95	87/13	78[b]
4	**3d**	n-Pr	≡—Ph	**4d**	90	98/2	78[c]
5	**3e**	$PhCH_2$	≡—Ph	**4e**	92	96/4	85[c]
6	**3f**	$PhCH_2$	Ph	**4f**	95	98/2	89[b]
7	**3g**	$PhCH_2$	i-Pr	**4g**	92	94/6	80[c]
8	**3h**	$PhCH_2$	Me	**4h**	96	75/25	58[b]
9	**3i**	Chx	n-Pr	**4i**	95	97/3	88[c]

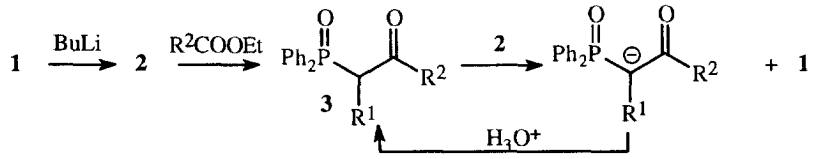
a) The anti/syn ratios were determined by ^{1}H NMR analysis.

b) The *anti*-isomers were isolated by flash cromatography (SiO_2, Et_2O/petroleum ether=9/1) or acetone/petroleum ether=2:1.

c) The *anti*-isomer was isolated by crystalization from THF/petroleum ether.

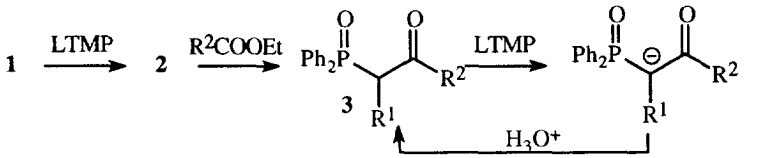
A typical procedure follows. $TiCl_4$ (1.5 eq., solution in CH_2Cl_2) was added to a solution of **2** in $CHCl_3$ or CH_2Cl_2 at -30°C. After 1h the mixture was cooled at -78°C and $LiBH_4$ (1.5 eq., solution in THF) was added. The reaction was stirred for 2h at this temperature, then allowed to reach room temperature and quenched with diluted HCl (10%). Usual work-up gave the crude product in high purity[8]. Most other reducing agents tried ($NaBH_4$, $LiBHEt_3$, REDAL) gave comparable diastereoselectivity, but lower yields and recovery of starting materials **3**, due to the more basicity of these reagents respect to $LiBH_4$.

β-Ketophosphine oxides **3** were previously prepared[4] (Scheme 2) by reaction of 1 eq of the suitable ester with 2 eq of the lithium derivative **2**, necessary for the complete conversion of the ester; infact 1 eq of **2** is consumed in the abstraction of the very acidic α-proton of the β-ketophosphine oxide. This procedure suffers from separation problems and low conversion of the most valuable product **2**.



Scheme 2

We modified this methodology (Scheme 3) by simply metalating **1** with 2.5 eq of a strong not nucleophilic base, such as lithiumtetramethylpiperidine (LTMP), which prevails over **2** in the metallation of **3**. In that manner anion **2** is exclusively involved in the reaction with the ester and β-ketophosphine oxides **3** are obtained in high yields based on **1**.

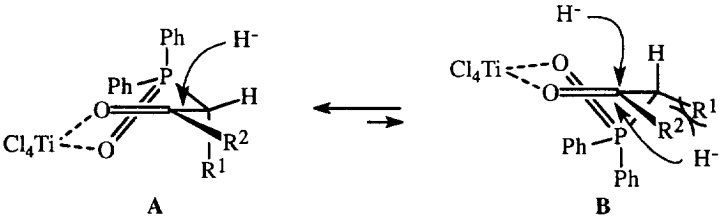


Scheme 3

A typical procedure follows. BuLi (2.3 eq) was added to tetramethylpiperidine (2.5 eq) at -30 °C. After 30 min product **1** (1 eq) was added and the mixture turned immediately to red. After 1h the mixture was cooled to -78°C and the ester (2.5 eq) was added. Two hours later, the reaction was allowed to reach room temperature and quenched with diluted HCl (10%). Usual work-up and crystallization from THF gave product **3** in high purity. β-ketophosphine oxides **3** were obtained in the following yields: **3a** 88%, **3b** 87%, **3c** 77%, **3d** 79%, **3e** 75%, **3f** 90%, **3g** 85%, **3h** 90%. This method as well as the previously reported procedures completely fails when R^1 is a branched alkyl substituent. Compound **3i** was prepared *via* oxidation of the mixture of *anti* and *syn* **4i** obtained by addition of the lithium salt of (cyclohexylmethyl)diphenylphosphine oxide to butyraldheyde[5].

In conclusion, a new approach to a very efficient synthesis of *anti*-β-hydroxyphosphine oxides has been successfully experimented. This new protocol offers the advantage over the previous ones of being unidirectional independently from the size of the alkyl substituents R^1 and R^2. The efficiency of this methodology can be very likely ascribed to the chelation control on the β-ketophosphine oxide system exerted by $TiCl_4$, whose O-chelating

power has been widely described for similar dioxygenated systems[7]. In other words, the six-membered complex between $TiCl_4$ and **3** is reasonably arranged in a preferential half-chair conformation[10] with R^1 in pseudo-axial position (**A**, Scheme 4) in order to minimize steric interactions between R^1 and R^2 groups. The attack of the reducing agent occours at the less hindered side of chelate **A** leading to the *anti* reduction product.



Scheme 4

Studies are in progress to generalize this procedure to the synthesis of β-hydroxyphosphine oxides containing hetero-substituted alkyl chains.

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8. The structure of products *syn*-**4** and *anti*-**4** was determined by ^1H and ^{13}C NMR analysis and furtherly verified by stereospecific decomposition with NaH in DMF to give the corresponding Z-olefins[4]. The structure of the unknown olefin derived from **4d** was determined by ^1H NMR ($J_{HHolefinic}$=10.7 Hz). Poor results were obtained for compounds **4e-h** containing a $PhCH_2$- group which gave the desired olefin in very low yields. This behaviour is quite surprising: infact in the synthesis of trisubstituted olefins[9] no problem was found in the decomposition of products carrying a benzylic group
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