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# Cerium Chloride (III) promoted Nucleophilic Addition of Organolithium Reagents to α-Diphenylphosphinoyl Ketones. An Efficient Method for the Synthesis of Horner-Wittig Intermediates

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**Abstract:** Reaction of α-diphenylphosphinoyl ketones with organolithium reagents, in the presence of anhydrous $CeCl_3$ in THF at -78°C, affords β-hydroxyalkylphosphine oxides in fair to good yields. These are essential to obtain olefins with β-carbon disubstituted.

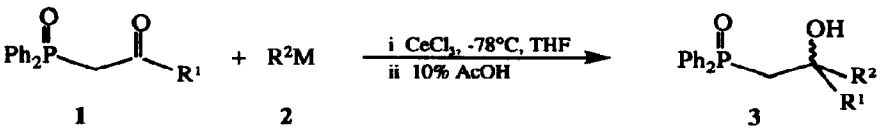
The Wittig reaction is one of the most versatile methods for the synthesis of olefins[1]. However this type of reactions proceeds with moderate yields, and in addition it shows uncomplete stereocontrol on the geometry of the double bond of the olefin produced[2,3]. A substantial improvement can be obtained with Horner-Wittig modification which eliminate $Ph_2PO_2^-$ in base to give olefins with greater stereocontrol[4,5]. The key intermediates of this Horner-Wittig reaction are the β-hydroxyalkylphosphine oxides prepared by reduction of α-diphenylphosphinoyl ketones or by nucleophilic addition of the anions of alkyl(diphenyl)phosphine oxide to carbonyl compounds. Nevertheless, very serious problems there are to synthetize by ketone addition Horner-Wittig intermediates with tertiary β-hydroxy group , essential to obtain olefins with β-carbon atom disubstituted. In fact, the anion reaction enolisation on the ketone often prevails[6]. In order to remedy these drawbacks we wish to describe in this letter an efficient method for the preparation of important β-hydroxyalkylphosphine oxides by the use of RLi-$CeCl_3$ reagent system.

Recently we reported that Grignard reagents can be directly added to 1,3-diketones and to β-enamino ketones, in the presence of dry $CeCl_3$ affording β-hydroxy ketones[7] and α,β-unsaturated ketones[8] respectively in excellent yields. This discovery prompted us to investigate this procedure with other enolisable substrates such as α-diphenylphosphinoyl ketones, which easily prepared by reaction of acylation[5] of diphenylmethylphosphine oxide or by reaction of alkylation of the dianion of α-diphenylphosphinoyl ketones[9]. Adding α-diphenylphosphinoyl ketones **1** at -78°C to organometallic reagents **2** in the presence of dry $CeCl_3$ at -78°C, followed by acidic quenching[10], directly affords β-hydroxyalkylphosphine oxide **3** (Table 1).

Grignard reagents (M= MgBr), with the exception of allylmagnesiumchloride, poor yields of product are accompanied by recovered starting material. This result is probably due to their greater speed of enolisation

versus nucleophilic addition to carbonyl group. Exchanging Grignard reagents for organolithium reagents the yields change from poor to good. Since little is known about the structure of organocerium compounds, this amazing outcome can

**Table 1** Reaction of α-dphenylphosphinoyl ketones **1** with organometallic regents **2** in the presence of $CeCl_3$ in THF at -78°C




**1** **2** **3**

| Entry | $R^1$ | $R^2M$ | Yield (%)[a] 3 |
|---|---|---|---|
| a | Me | MeLi | 72.5 |
| b | Me | EtLi | 71.0 |
| c | Me | $Pr^nLi$ | 67.0 |
| d | Me | $Bu^nLi$ | 82.5 |
| e | Me | $Bu^sLi$ | 78.5 |
| f | Me | Li-1,3-dithiane | 67.3 |
| g | Me | AllylMgCl | 86.4 |
| h | $Bu^n$ | MeLi | 65.0 |
| i | $Bu^n$ | AllylMgCl | 85.7 |
| l | Me | PhLi | 76.2[b] |

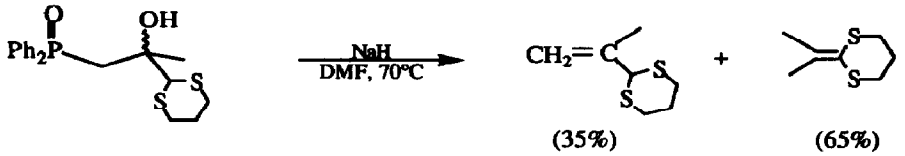
[a]Yield of pure, isolated products. [b]Product dehydrated only

be tentatively rationalized by postulating effective species organocerium reagents are obtained by transmetallation reactions from organolithiums[11] only. In fact this process proceeds slowly at 0°C for organomagnesiums, then at -78°C it would be practically ineffective so that a reactive species of type $RMgX:CeCl_3$ is postulated[12].

The presence of cerium chloride is essential for the success of this procedure since a rapid deprotonation of the active methylene hydrogens is normally observed in its absence. The resulting enolate exhibits an extremely stable cyclic structure with a pseudo-aromatic array and hence it is completely inert towards nucleophilic attack[13]. Similar behaviour is shown by α-diphenylphosphinoyl ketones 'pre-worked' with cerium chloride before the addition of the organolithium reagent, leading, after quenching, to the unchanged starting material.

The examples displayed in table 1 effectively shows the peculiarity of this procedure, which can be used to

introduce a large variety of carbon frameworks, in the preparation of tertiary β-hydroxyalkylphosphine oxides[14]. Then they easily give olefins on elimination with NaH in DMF[15] (Scheme 1).




**Scheme 1**

The reaction of α-diphenylphosphinoylpropan-2-one with PhLi-$CeCl_3$ (Entry l) is also worthy to mention. In contrast to the other examples it produce after usual workup 3-diphenylphosphinoyl-2-phenylprop-1-ene as the only product.

In summary we have developed an efficient method for the synthesis of β-hydroxyalkylphosphine oxides; the mild reaction conditions and use of non-toxic cerium chloride render this method synthetically useful and a complete study on the synthetic potentialities of this procedure for the stereoselective synthesis of important trisubstituted olefins is currently in progress in our laboratories.

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10. *Typical experimental procedure is as follows:* Finelly ground $CeCl_3 \cdot 7H_2O$ (2.6 g, 7.0 mmol) is dried by heating at 140°C, 0.1 Torr for 2h. Dry THF (40 ml) is then added at 0°C and the milky suspension is stirred overnight under nitrogen at room temp. The organolithium reagent (7.0 mmol) is then added at -78°C and the mixture is stirred for 2h at the same temperature. The α-diphenylphosphinoyl ketone (1.4 mmol), dissolved in dry THF (15 ml) is then added dropwise at -78°C, the mixture is stirred at this temperature for 1h and then allowed to warm to 0°C very slowly. The reaction mixture is quenched by addition of 10% aqueous acetic acid (45 ml). Usual work-up gives the crude product which is purified by column chromatography (hexane-ethyl acetate 1:9).
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14. Characterization data for some of the new compounds prepared follows:

    **3b:** m.p. 253-255°C (from AcOEt), IR ($cm^{-1}$, nujol): 3400 (OH), 1185 (P=O); $^1$H-NMR (300MHz,

$CDCl_3$) δ (ppm): 0.85 (t, 3H, J= 7.4Hz); 1.20 (s, 3H), 1.63 (q, 2H, J= 7.3Hz), 2.55 (2d, 2H, $J_{HP}$= 10.1 and 9.6Hz), 4.95 (s, 1H, OH), 7.35-7.85 (m, 10H, arom.); MS m/z: 288 ($M^+$), 273, 270, 260, 259, 215, 201, 77, 65.

**3c:** m.p. 281-283°C (from AcOEt), IR ($cm^{-1}$, nujol): 3385 (OH), 1180 (P=O); $^1$H-NMR (300MHz, $CDCl_3$) δ (ppm): 0.78 (t, 3H, J= 7.1Hz), 1.15-1.40 (m, 5H), 1.55 (t, 2H, J= 7.0Hz), 2.55 (2d, 2H, $J_{HP}$= 10.0 and 9.6Hz), 4.98 (s, 1H, OH), 7.40-7.85 (m, 10H, arom.); MS m/z: 302 ($M^+$), 284, 259, 215, 201, 77, 65.

**3d:** m.p. 290-292°C (from AcOEt), IR ($cm^{-1}$, nujol): 3365 (OH), 1175 (P=O); $^1$H-NMR (300MHz, $CDCl_3$) δ (ppm): 0.85 (t, 3H, J= 7.2Hz), 1.10-1.40 (m, 7H), 1.60 (t, 2H, J= 6.5Hz), 2.50 (2d, 2H, $J_{HP}$= 10.1 and 9.7Hz), 5.05 (s, 1H, OH), 7.40-7.85 (m, 10H, arom.); MS m/z: 298 ($M^+$-18), 269, 215, 201, 77.

**3e:** oil, IR ($cm^{-1}$, neat): 3350 (OH), 1165 (P=O); $^1$H-NMR (300MHz, $CDCl_3$) δ (ppm): 0.65 (t, 3H, J= 7.1Hz), 0.95 (d, 3H, J= 7.4Hz), 1.15 (s, 3H), 1.40-1.55 (m, 2H), 1.75-1.85 (m, 1H), 2.55 (2d, 2H, $J_{HP}$= 10.1 and 9.9Hz), 4.95 (s, 1H, OH), 7.35-7.85 (m, 10H, arom.); MS m/z: 300 ($M^+$-18), 259, 215, 201, 77.

**3f:** m.p. 265-268°C (from $CH_2Cl_2$-Esano), IR ($cm^{-1}$, nujol): 3310 (OH), 1175 (P=O); $^1$H-NMR (300MHz, $CDCl_3$) δ (ppm): 1.40 (s, 3H), 2.20-2.85 (m; 6H), 3.05 (2d, 2H, $J_{HP}$= 10.1 and 9.7Hz), 4.20 (s, 1H), 5.25 (s, 1H, OH), 7.40-7.85 (m, 10H, arom.); MS m/z: 360 ($M^+$-18), 259, 215, 201, 159, 119, 77.

**3g:** oil, IR ($cm^{-1}$, neat): 3380 (OH), 1175 (P=O); $^1$H-NMR (300MHz, $CDCl_3$) δ (ppm): 1.25 (s, 3H), 2.30 (d, 2H, J= 7.0Hz), 2.55 (2d, 2H, $J_{HP}$= 10.1 and 9.5Hz), 4.90-5.10 (m, 2H, $CH_2$=), 5.35-5.90 (m, 2H, -CH= and OH), 7.45-7.85 (m, 10H, arom.); MS m/z: 282 ($M^+$-18), 259, 215, 201, 77, 65, 41.

**3i:** oil, IR ($cm^{-1}$, neat): 3375 (OH), 1180 (P=O); $^1$H-NMR (300MHz, $CDCl_3$) δ (ppm): 0.75 (t, 3H, J= 7.3Hz), 0.95-1.60 (m, 6H), 2.30 (d, 2H, J= 7.3Hz), 2.55 (2d, 2H, $J_{HP}$= 10.2 and 9.8Hz), 4.85-5.00 (m, 2H, $CH_2$=), 5.08 (s, 1H, OH), 5.65-5.85 (m, 1H, -CH=), 7.40-7.85 (m, 10H, arom.); MS m/z: 324 ($M^+$-18), 301, 285, 216, 201, 77, 65, 41.

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