Reduction of activated carbonyl groups by alkyl phosphines: formation of α-hydroxy esters and ketones†

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Reduction of activated carbonyl groups such as α-keto esters, benzils, 1,2-cyclohexanedione, and α-ketophosphonates by alkyl phosphines afforded the corresponding α-hydroxy esters or ketones in good to excellent yields in THF at room temperature. The mechanism of the proton transfer and intramolecular hydrolysis has been studied on the basis of deuterium and ^{18}O labeling experiments.

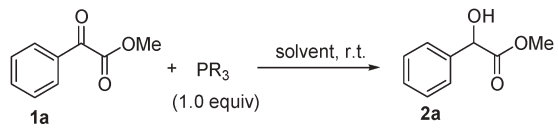
α-Hydroxy esters are important synthetic intermediates, especially in the field of bioactive molecule synthesis, that can be obtained through transition metal catalyzed hydrogenation,[1] bioreduction with baker's yeast reductase or *Escherichia coli* cells,[2] and chemical reduction by β-chlorodiisopinocampheylborane,[3] titanium(II) porphyrin complexes[4] or sodium dithionite.[5] While phosphines are widely used as Lewis bases or ligands in organic chemistry,[6] to our knowledge, the Staudinger reaction was the early report on the reduction of azides to amines by Ph_3P/H_2O,[7] no report regarding their use as reductants accompanied with a proton movement has been published. Herein, we report the reduction of activated carbonyl groups in α-keto esters, benzils, 1,2-cyclohexanedione and α-ketophosphonates by alkyl phosphines, such as trimethylphosphine or diphenylmethylphosphine, under mild conditions to form the corresponding α-hydroxy esters, ketones and phosphonates.

An initial examination was carried out by the reaction of methyl phenylglyoxylate (**1a**) (1.0 equiv.) with trimethylphosphine[8] (PMe_3) (1.0 equiv.) in THF at room temperature. We found that reduction took place to give the corresponding hydroxy–phenyl–acetic acid methyl ester (**2a**) in 75% yield within 2 h (Table 1, entry 1) and using 0.5 equiv. of PMe_3, resulted in **2a** being obtained in only 39% yield under identical conditions (Table 1, entry 2). Molecular sieves did not affect the reduction, (Table 1, entry 3) and using PPh_2Me, $PPhMe_2$, or PBu_3 as reductants prolonged the required reaction times (Table 1, entries 4–6). Both PPh_3 and $P(OEt)_3$ showed no reaction (Table 1, entries 7 and 8). These results suggest that aliphatic substituents of the phosphine are necessary for reduction to occur. Solvent effects were also examined for reactions PPh_2Me and $PPhMe_2$ (Table 1, entries 9–16). For example, we observed that **2a** was obtained in 70% yield with 1.0 equiv. of PPh_2Me in methanol after 48 h. Overall, the best result was obtained by using PMe_3 as the reductant for 2 h in THF.

Using these optimized conditions, we next examined the reactions of a variety of α-keto esters with PMe_3 or PPh_2Me. The results are summarized in Table 2. Aryl group substituted α-keto esters produced the corresponding reduction products **2** in good yields (Table 1, entries 1–6). The electron-donating substrate **1g**, which was reduced to **2g** in low yield by biocatalysis,[9] was obtained reduced in 71% yield using this reduction method (Table 2, entry 6). For substrates having two substituents on the benzene ring such as (3,5-dimethylphenyl)-oxo-acetic acid ethyl ester (**1h**), the reaction proceeded smoothly under identical reactions to give the corresponding product **2h** in 71% yield (Table 2, entry 7). Alkyl group substituted α-keto esters **1i–k** afforded products **2i–k** in excellent yields (Table 2, entries 8–10).

Furthermore, the reduction of benzils (**3a–d**) to benzoins (**4a–d/4a″–d″**) proceeded smoothly under the standard conditions to give the corresponding reduced products in high yields and various moderate selectivities (Table 3, entries 1–4). In addition, for 1,2-cyclohexanedione **3e**, the corresponding reduced product **4e** was obtained in 80% yield (Table 3, entry 5).

Table 1 Reduction of methyl phenylglyoxylate **1a** by various phosphines in a variety of solvents[a]



1a **2a**

Entry	PR_3	Solvent	Time/h	**2a** (%)[b]
1	PMe_3	THF	2	75
2[c]	PMe_3	THF	2	39
3[d]	PMe_3	THF	2	72
4	PPh_2Me	THF	48	60
5	$PPhMe_2$	THF	48	54
6	PBu_3	THF	48	24
7[e]	PPh_3	THF	72	N.R.
8[e]	$P(OEt)_3$	THF	72	N.R.
9	$PPhMe_2$	$PhCH_3$	48	40
10	$PPhMe_2$	Et_2O	48	46
11	$PPhMe_2$	CH_3CN	48	24
12	$PPhMe_2$	MeOH	48	48
13	$PPhMe_2$	1,4-dioxane	48	54
14	$PPhMe_2$	—	72	trace
15	PPh_2Me	MeOH	48	70
16	PPh_2Me	1,4-dioxane	48	36

[a] Methyl phenylglyoxylate (0.3 mmol), phosphine (0.3 mmol) and solvent (0.3 mL, 1.0 M) were used. [b] Isolated yields. [c] 50 mol% of trimethyl phosphine was used. [d] Molecular sieves 4A were used. [e] No reaction occurred.

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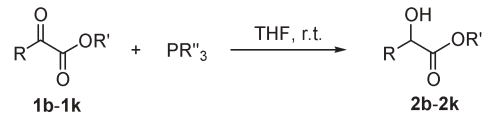
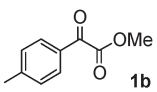
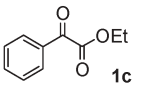
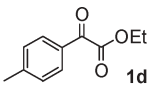
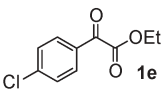
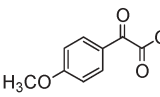
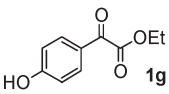
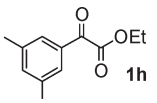
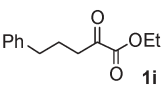
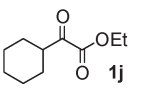
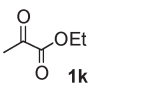
† Electronic supplementary information (ESI) available: ^{13}C and ^{1}H NMR spectroscopic data for compounds **2a–2k**, **4a–4e**, **6**, **8** and **10** and deuterium and ^{18}O labeling experiments, spectroscopic trace study for the reaction system. See DOI: 10.1039/b516467b

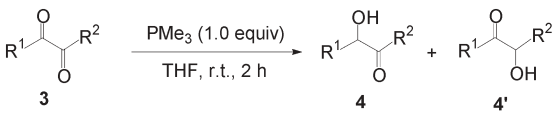
Table 2 Reduction of α-keto esters with trimethylphosphine or diphenylmethylphosphine in THF at room temperature[a]



Entry	1	Phosphine (PR''_3)	Time/h	2	(%)[b]
1		PMe_3	2	**2b**	81
		PPh_2Me[c]	48	**2b**	69
2		PMe_3	2	**2c**	81
		PPh_2Me[c]	48	**2a**	80[d]
3		PMe_3	2	**2d**	85
4		PMe_3	2	**2e**	81
5		PMe_3	2	**2f**	85
6		PMe_3	2	**2g**	71
7		PMe_3	2	**2h**	71
8		PMe_3	2	**2i**	80
9		PMe_3	2	**2j**	96
10		PMe_3	2	**2k**	97[e]

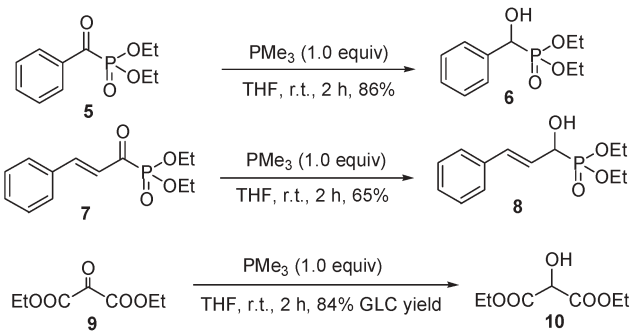
[a] **1** (0.3 mmol), phosphine (0.3 mmol) in THF (0.3 mL) were stirred at room temperature. [b] Isolated yields. [c] MeOH was used as solvent. [d] The product was **2a**. [e] GLC yield.

Table 3 Reduction of benzils and 1,2-cyclohexanedione with trimethylphosphine



Entry	R^1	R^2	Products	Yield (%)[a](ratio **4/4′**)[b]
1	C_6H_5	C_6H_5 **3a**	**4a**	84
2	C_6H_5	4-FC_6H_4 **3b**	**4b/4b′**	85 (1.2/1)
3	C_6H_5	4-$MeOC_6H_4$ **3c**	**4c/4c′**	93 (5.5/1)
4	C_6H_5	CH_3 **3d**	**4d/4d′**	73 (1.4/1)
5	$-C_4H_8-$ **3e**		**4e**	80

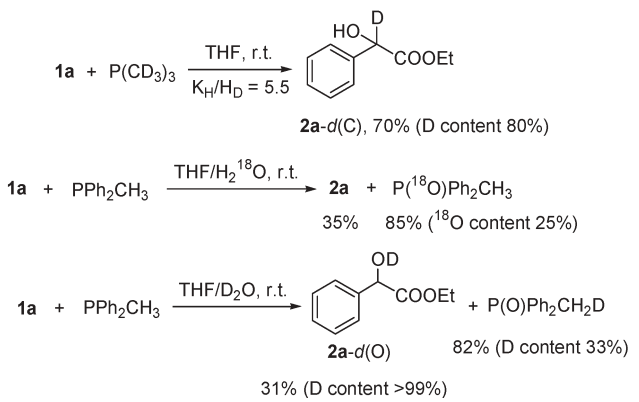
[a] Isolated yields. [b] The ratio of **4/4′** was determined by ^{1}H NMR spectrum.



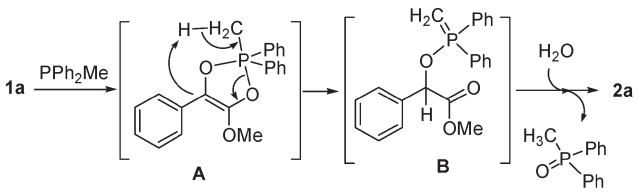
Scheme 1 Reduction of functionalized ketones with trimethylphosphine.

On the other hand, the reduction of α-ketophosphonates **5** and **7** and diethyl ketomalonate **9** also proceeded smoothly to give the corresponding reduced products **6**, **8**, and **10**, respectively, in good yields (Scheme 1). It should be noted that the alkene group in **7** remained unchanged under these reduction conditions.

In order to identify the proton source in these reactions, the reduction of **1a** with trimethylphosphine-*D*,[9] prepared from reaction of CD_3MgI with tri-*o*-tolyl phosphite,[10] was carried out under the standard conditions and the product of **2a**-*D*(C) was produced in 70% isolated yield with 80% D incorporation at the C_1 position (Scheme 2).[11] A primary isotope effect was of $k_H/k_D \approx 5.5$ was observed.[12] This result suggests that only one proton is directly transferred from trimethylphosphine to product **2a**, and an additional equivalent of water is required for the release of the phosphorus atom through formation of the phosphine oxide during work-up. Other control experiments were carried out by adding one equivalent of D_2O (D content = 99.8%) and $H_2{}^{18}O$ (^{18}O content = 94.1%) into the PPh_2Me/THF reduction system, respectively. We found that in the presence of $H_2{}^{18}O$, **2a** was formed in 35% isolated yield along with 85% of $P(^{18}O)Ph_2CH_3$, in which ^{18}O content is 25%, as determined by EI-MS. In the presence of D_2O, **2a**-*d*(O) was formed in 31% yield (D content > 99%), along with $P(O)Ph_2CH_2D$ in 82% isolated yield (D content 33%), as determined by ^{1}H NMR analysis.[13] Therefore, the observed ^{18}O and D contents are consistent with the formation of **2a**. The excess formation of the corresponding phosphine oxide is most likely due to the oxidation by the ambient oxygen during



Scheme 2 Isotope labeling experiments.



Scheme 3 A possible reaction mechanism.

work-up (see Figures SI-8 to SI-19 in the Supporting Information†).[14]

The proposed mechanism based on the observed results of this interesting reaction is outlined in Scheme 3. Initially, coordination of two oxygen atoms in **1a** to the phosphorus atom of diphenylmethylphosphine takes place to give intermediate A according to the literature.[15] The intramolecular proton transfer from the methyl group of the phosphine to the corresponding activated carbonyl group produces intermediate B, which subsequently undergoes O–P bond cleavage by ambient moisture or during work-up to generate **2a** and the corresponding phosphine oxide. It should be noted that activated (by carbonyl or phosphoryl groups) carbonyl groups are essential for this reduction because no reaction occurred using phenylethanone or β-keto esters as the substrate under the standard conditions.

In summary, we have presented the reduction of α-keto esters, benzils, 1,2-cyclohexanedione and α-ketophosphonates by alkyl phosphines (trimethylphosphine and diphenylmethylphosphine) in THF or methanol at room temperature. This reaction system has wide application on reduction of substituted aryl phenylglyoxylates. On the basis of the deuterium and ^{18}O labeling experiments, we found that this reaction proceeds through a proton transfer from the alkyl phosphine and cleavage by H_2O during work-up. Efforts are in progress to further confirm mechanistic details of this reaction and to understand its scope and limitations.†

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10 R. T. Li, S. T. Nguyen, R. H. Grubbs and J. W. Ziller, *J. Am. Chem. Soc.*, 1994, **116**, 10032–10040; CD_3MgI was prepared from CD_3I (D content > 90%) with magnesium.

11 The D content of **2a**–*d*(C) was determined by ^1H NMR spectrum (Please see the Supporting Information).

12 The equations of the initial stage within 40 minutes were $Y = 6.2X + 68.37$ for the $P(CH_3)_3$ system and $Y = 1.125X + 40.50$ for the $P(CD_3)_3$ system (Please see the Supporting Information).

13 The comparable reaction was carried out under identical conditions by adding one equivalent of unlabeled H_2O. We found that **2a** was obtained in 48% yield along with 52% of the starting materials **1a** and 81% yield of the corresponding $P(O)Ph_2Me$.

14 PPh_2Me is very air sensitive in ambient atmosphere and can easily be oxidized to $P(O)Ph_2Me$ during flash column chromatography.

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