

Phosphine-Catalyzed Hydration and Hydroalkoxylation of Activated Olefins: Use of a Strong Nucleophile to Generate a Strong Base

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β -Hydroxy ketones are ubiquitous intermediates and targets in organic synthesis. They are typically prepared either via aldol chemistry or sequential epoxidation and reduction of enones.^{1,2} Direct preparation by addition of water to an enone is an attractive alternative, but no method exists for this transformation. Similarly, preparation of β -alkoxy ketones also represents a challenge in synthetic organic chemistry. Although methods exist for their synthesis from enones,^{3–5} direct preparation via alcohol addition would be ideal, but has not yet been generally realized.⁶ Trost⁷ and Inanaga,⁸ however, have reported catalytic methods for the addition of alcohols to alkynoates. Herein we report a general method for the hydration and hydroalkoxylation of enones and other α,β -unsaturated substrates by use of a trialkylphosphine catalyst.

During investigations into a transition metal-catalyzed hydration reaction, we discovered that the phosphine ligand alone was actually a more active catalyst. In the presence of catalytic amounts of trimethylphosphine, we observed the direct addition of water and alcohols to α,β -unsaturated compounds in quantitative conversion. A number of potential Lewis basic catalysts were tested using the hydromethoxylation of **1** as a benchmark (Table 1). Trialkylphosphines (Table 1, entries 1–3) were more reactive than aryl phosphines (Table 1, entries 4–6) and nitrogen-based nucleophiles (Table 1, entries 7–8).

A variety of α,β -unsaturated substrates were subjected to hydromethoxylation conditions.⁹ Enones, α,β -unsaturated esters, and α,β -unsaturated nitriles all provided the corresponding hydromethoxylated products in good isolated yields. Only the highly conjugated 4-phenyl-3-buten-2-one was unreactive, even at increased temperatures and reaction times (Table 2, entry 7).¹⁰ Cyclic enones were found to undergo competitive dimerization reactions in both the hydration and hydromethoxylation conditions.

Using **1** and methyl vinyl ketone as our standard enones, the scope of reactive hydroxyl compounds was shown to include water and primary, secondary, and aryl alcohols. *tert*-Butyl alcohol did not undergo addition to either **1** or methyl vinyl ketone; instead, enone dimerization was observed.¹¹ Surprisingly, no retro-aldol or ketalization products were ever observed in these reactions. In contrast, the rates of retro-aldol reactions are competitive with hydration in analogous base-catalyzed systems.¹²

On the basis of experiments described below, we propose the catalytic cycle shown in Scheme 1.^{13,14} Initial conjugate addition by the phosphine to the unsaturated carbonyl compound results in formation of phosphonium enolate **3**, which deprotonates an equivalent of alcohol. The alkoxide of ion pair **4** then undergoes a subsequent conjugate addition, generating enolate ion pair **5**.¹⁵ Protonation of the enolate partner in **5** results in formation of the β -alkoxy carbonyl and regeneration of **4** to complete the cycle.

An alternative mechanism in which trimethylphosphine ($pK_a = 9$)¹⁶ functions simply as a base to deprotonate the alcohol directly is also possible. However, when catalysis was attempted with

Table 1. Catalyst Survey^a

entry	catalyst	time (h)	T (°C)	% conv. ^b
1	PMe ₃	6	45	95
2	PBu ₃	6	45	95
3	Me-BPE ^c	4	45	93
4		20	105	45
5	<i>rac</i> -BINAP ^d	18	75	0
6	Et-DuPhos ^e	22	75	0
7	quinuclidine ^f	48	45	54
8	DABCO ^{f,g}	16	45	0
9	Et ₃ N ^f	25	45	0
10	O=PMe ₃ ^f	20	45	0

^a Reaction conditions: 1 mmol 4-hexen-3-one, 0.05 mmol catalyst in 0.3 mL CD₃OD. ^b Determined by ¹H NMR spectroscopy. ^c Me-BPE = 1,2-bis(2,5-dimethylphospholano)ethane. ^d BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl. ^e Et-DuPhos = 1,2-Bis(2,5-diethylphospholano)benzene. ^f 10 mol % catalyst. ^g DABCO = bicyclo[2.2.2]-1,4-diazaoctane.

Table 2. Phosphine-Catalyzed Hydration and Hydroalkoxylation^a

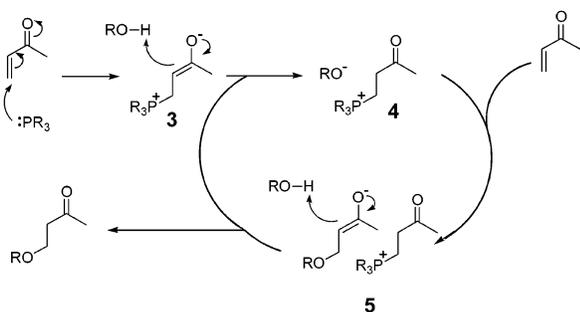
entry	EWG	R ¹	ROH	time (h)	% yield ^b
1	COEt	Me	H ₂ O	20	77
2			MeOH	24	85
3 ^c				16	63
4	COMe	H	MeOH	1	56
5 ^c			Me ₂ CHOH	1	83
6 ^c			PhOH	16	59
7		Ph	MeOH	72	0
8	CO ₂ Me	Me	MeOH	36	71
9	CN	H	MeOH	4	79

^a Reaction conditions: see ref 9. ^b Isolated yield after purification. ^c Run in CH₃CN.

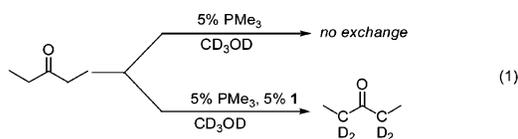
triethylamine ($pK_a = 11$)¹⁷ (Table 1, entry 9), no product was observed by ¹H NMR spectroscopy. Additionally, the ease with which trialkylphosphines are oxidized suggests that phosphine oxide might be the active catalyst; this was also shown not to be the case (Table 1, entry 10).

When deuterated protic solvents were used in these reactions, H/D exchange was observed at both of the α -positions of the α,β -unsaturated compound. This suggested that a strong base is

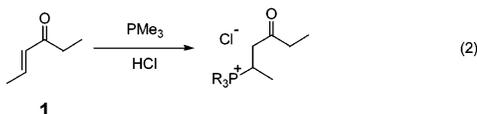
Scheme 1. Proposed Catalytic Cycle



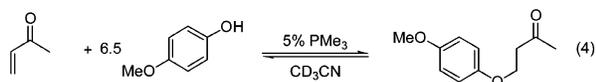
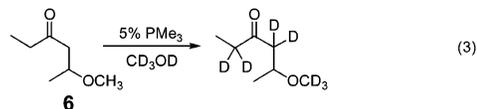
generated during the reaction. Trimethylphosphine alone did not facilitate H/D exchange of 3-pentanone, indicating that it alone is not the active catalyst. However, addition of a catalytic amount of an enone *and* trimethylphosphine caused rapid H/D exchange at the α -positions (eq 1), clearly supporting the base-generation hypothesis.



The resting state of the catalyst was investigated by ^{31}P NMR spectroscopy. When **1** was subjected to a catalytic amount of PMe_3 in hydroxylic solvents, a single ^{31}P NMR resonance at 33 ppm was observed. This suggested the presence of a β -phosphonium ketone,¹⁸ which is consistent with **4** being the resting state of the catalyst in our proposed mechanism.¹⁹ This β -phosphonium ketone was independently synthesized by addition of a full equivalent of PMe_3 to **1** in the absence of hydroxylic solvents, followed by addition of HCl (eq 2). The ^{31}P NMR resonance of this phosphonium salt matched that observed in the catalytic reactions.



Exchange experiments and variable temperature NMR spectroscopy were employed to investigate the reversibility of this reaction. β -Methoxy ketone **6** readily undergoes exchange with perdeuteriomethanol in the presence of 5% PMe_3 , suggesting that the reaction is reversible (eq 3).²⁰ Variable-temperature NMR spectroscopy was employed to determine the thermodynamic parameters associated with this equilibrium. *p*-Methoxyphenol was chosen for the study because it gave rise to an observable ratio of unreacted enone to product at room temperature (eq 4). As expected on the basis of



entropy considerations, the ratio of starting materials to products was increased by raising the temperature from 25 to 75 °C. Upon cooling, the system returned to its original distribution. A van't

Hoff plot confirmed that the reaction was exothermic and entropically disfavored ($\Delta H^\circ = -5.0$ kcal/mol and $\Delta S^\circ = -18$ eu).

In conclusion, we have shown that nucleophilic phosphines in the presence of α,β -unsaturated systems can be used to catalyze the hydration and hydroalkoxylation of activated olefins in the absence of added transition metals, or strong acids or bases. This transformation contrasts the recently reported catalysis of the Baylis–Hillman reaction of bis(enones) by trialkylphosphines.^{21,22} Our proposed catalytic cycle suggests that this very practical system could be extended to other classes of nucleophiles with pK_a 's matched to that of the enolate intermediates. Additionally, the possibility of using other nucleophilic catalysts would further extend the applicability and practicality of this genre of reactivity.

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Note Added after ASAP: There was an error in Scheme 1 in the version published on the Web 6/18/2003. The version published 6/20/2003 and the print version are correct.

Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge on the Internet at <http://pubs.acs.org>.

References

- Ryberg, P.; Matsson, O. *J Am. Chem. Soc.* **2001**, *123*, 2712–2718.
- Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287–1290.
- Pd-catalyzed hydration: (a) Ganguly, S.; Roundhill, D. M. *Organometallics* **1993**, *12*, 4825–4832. Pd-catalyzed hydroalkoxylation: (b) Miller, K. J.; Kitagawa, T. T.; Abu-Omar, M. M. *Organometallics* **2001**, *20*, 4403–4412.
- Use of high pressure for olefin hydration: Jenner, G. *Tetrahedron Lett.* **2001**, *42*, 4807–4810. Jenner, G. *Tetrahedron* **2002**, *58*, 4311–4317.
- Kabashima, H.; Katou, T.; Hattori, H. *Appl. Catal., A* **2001**, *214*, 121–124.
- For progress towards a general method, see: Kisanga, P. B.; Ilankumaran, P.; Fetterly, B. M.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 3555–3560.
- Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819–10820.
- Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, *2*, 241–4.
- Typical experimental procedure: 10 mmol of substrate in 10 mL of alcohol was subjected to three freeze–pump–thaw cycles, following which PMe_3 was added via vacuum-transfer. The flask was sealed and left for the time indicated. The reaction mixture was then filtered through a pad of silica and concentrated under reduced pressure. In the case of methanol addition the desired product was obtained in high purity without chromatography. All other reactions required flash column chromatography using mixtures of hexanes and ethyl acetate as the eluent to afford pure product.
- DFT calculations suggest that hydration of 4-phenyl-3-buten-2-one is less enthalpically favored.
- For another example of this, see: Allen, A. A.; Duffner, R.; Kurzer, F. *Tetrahedron* **1978**, *34*, 1247–1250.
- For an example of retro-aldol reactions in related systems, see: Jensen, J. L.; Hashtroudi, H. *J. Org. Chem.* **1976**, *41*, 3299–3302.
- For a related mechanism, see: White, D. A.; Baizer, M. M. *Tetrahedron Lett.* **1973**, *14*, 3597–3600.
- An alternative mechanism could involve direct displacement of PR_3 from the β -phosphonium ketone. Displacements of this type, however, are extremely rare.
- Addition of 5 mol % of NaOH or NaOMe to an aqueous or alcohol solution of enone also produced the corresponding hydroxylated or hydroalkoxylated product. See ref 11 for more on base-catalyzed hydrations and competing retro-aldol reactions.
- Henderson, W. A.; Streuli, C. A. *J. Am. Chem. Soc.* **1960**, *82*, 5791–5794.
- Bruice, P. Y. *J. Am. Chem. Soc.* **1984**, *106*, 5959–5964.
- Alt, H. G.; Hayen, H. I. *J. Organomet. Chem.* **1986**, *316*, 301–313.
- This observation is also consistent with **5** being the resting state; however, the **5** \rightarrow **4** proton transfer should be exothermic and rapid.
- A catalytic amount of enone is likely formed from elimination of methanol from 2-methoxy-4-hexanone. The mechanism of the elimination is not necessarily the microscopic reverse of the mechanism for the addition reactions described in Scheme 1.
- Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402–2403.
- Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405.

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