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Highly Efficient Synthesis of Quaternary α-Hydroxy Phosphonates *via* Lewis Acid-Catalyzed Hydrophosphonylation of Ketones

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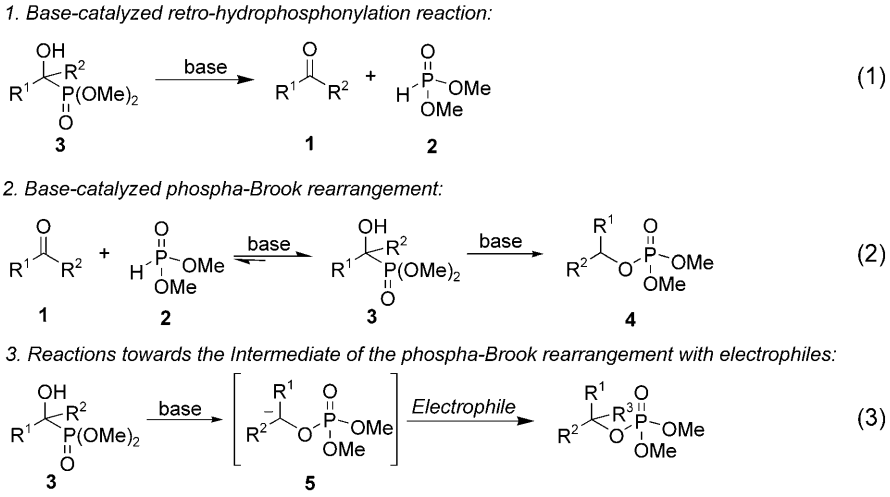
Abstract: A Lewis acid catalyst has been first applied to the hydrophosphonylation of ketones, giving the corresponding quaternary α-hydroxy phosphonates in high yields (up to 98%). The present method was highly tolerable for functionalized ketones. Moreover, the first catalytic enantioselective hydrophosphonylation of an unactivated ketone was also realized by using a tridentate Schiff base-titanium complex.

Keywords: asymmetric synthesis; functionalized ketones; hydrophosphonylation; ketones; titanium

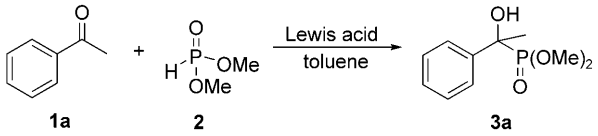
The α-hydroxy phosphonates have exhibited intriguing biological activities,[1] and are widely applied in pharmaceutical chemistry as bio-phosphate mimics,[2] antibiotics,[3] anti-virals[4] and anti-tumour agents.[5] Particularly, as analogues of quaternary α-hydroxy acids, the quaternary α-hydroxy phosphonates are of considerable value because they may potentially increase the rigidity and resistance to protease enzymes and enhance bioactivity. As a consequence, the synthesis of quaternary α-hydroxy phosphonates has attracted significant attention.[6] To the best of our knowledge, the hydrophosphonylation of ketones provides one of the most efficient methods for their preparation.[7] However, due to the low reactivity of ketones, an efficient catalyst for such a reaction was scarcely developed,[8] which was in sharp contrast to the hydrophosphonylation of aldehydes.[9] Whereas strong bases were hitherto the most general catalysts for the synthesis of quaternary α-hydroxy phosphonates,[10] the yields were not always good and mixtures of products were sometimes obtained due to the low reactivity of ketones, retro-hydrophosphonylation reactions [Scheme 1, Eq. (1)],[11] phospha-Brook rearrangements [Scheme 1, Eq. (2)][12] and so on [for example, Scheme 1, Eq. (3)].[13] Furthermore, the strong basic catalysts potentially excluded the hydrophosphonylation of base-sensitive ketones, even mild bases such as tertiary amines may also cause side reactions.[14] Thus, searching for a catalyst that could achieve high reactivity and wide applicability, especially for functionalized ketones, was still challenging and interesting. Since Lewis acids have long been proved to be effective for the hydrophosphonylation of aldehydes, it was surprising that they have never been applied in the reaction of ketones. It was surmised that a suitable Lewis acid could not only effectively activate the dialkyl phosphite and ketone but also potentially suppress or avoid the shortcomings of the base-catalyzed reaction. Moreover, the Lewis-acid catalyzed process could also provide the potential for an asymmetric version by incorporating a suitable chiral ligand. Herein, we describe the first Lewis acid-catalyzed, highly efficient hydrophosphonylation of ketones. The present method was suitable for a wide range of substrates, and especially for functionalized ketones. The first catalytic asymmetric hydrophosphonylation of acetophenone is also presented.

A preliminary survey revealed that the mildly acidic Ti(O-*i*-Pr)$_4$ was a promising catalyst for the hydrophosphonylation of acetophenone (Table 1, entry 1). With 5 mol% Ti(O-*i*-Pr)$_4$, the corresponding product was obtained with 58% isolated yield for 12 h. In contrast, other Lewis acids which were effective for the hydrophosphonylation of aldehydes or aldimines gave **3a** with $\leq$16% yield (Table 1, entries 2–8).[15a]



Scheme 1. Towards related reactions for the hydrophosphonylation of ketones.

Table 1. Catalytic hydrophosphonylation of acetophenone.[a]



Entry	Metal	Yield [%]	Entry	Metal	Yield [%]
1	$Ti(O\text{-}i\text{-}Pr)_4$	58	2	$Al(O\text{-}i\text{-}Pr)_3$	6
3	$In(OTf)_3$	16	4	$Sc(OTf)_3$	12
5	$Yb(OTf)_3$	10	6	$La(OTf)_3$	7
7	$TiCl_4$	N.R[b]	8	$Zr(O\text{-}i\text{-}Pr)_4$	N.R[b]

[a] Reactions were carried out with **1a** (0.5 mmol), **2** (100 μL) and Lewis acid (5 mol%) in toluene (1.0 mL) at 23 °C for 12 h.
[b] No reaction occurred.

An intensive investigation of the reaction conditions revealed that the concentration of acetophenone played a crucial role on the reactivity (Figure 1).[15b] By increasing the concentration of acetophenone, the yield was dramatically improved. The hydrophosphonylation of acetophenone was complete within 10 min under neat conditions.[15c] In sharp contrast to such solvent-free conditions, when the reaction was per-

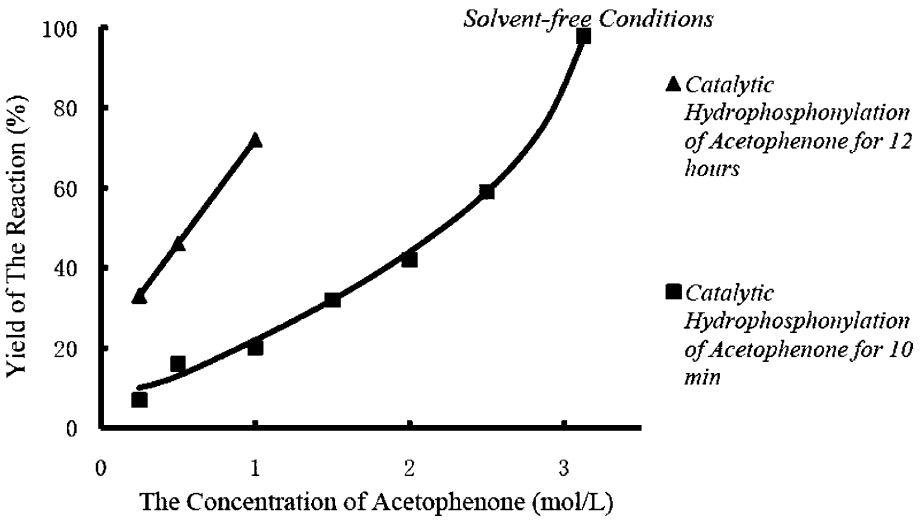


Figure 1. The concentration effect in the hydrophosphonylation of acetophenone.[16a]

formed at a low concentration of acetophenone ($c \leq$ 1.0 mol/L), the quaternary α-hydroxy phosphonate **3a** was only obtained with poor to moderate yield (33–72%) albeit with a prolonged reaction time (12 h).[15d]

The substrate scope of catalytic hydrophosphonylation of ketone was then investigated under solvent-free conditions, and the corresponding quaternary α-hydroxy phosphonates were obtained with high yields (Figure 2).[17] Irrespective of the electronic nature of the aryl substituents and their location, the reaction of aromatic ketones showed high reactivities (products **3a–j**). The current system could be further extended to the hydrophosphonylation of condensed ring, diaryl, conjugated and heteroaromatic ketones, giving the corresponding products with up to 95% yield (products **3k–o**). The aliphatic ketones were also effective substrates for the reaction albeit with reduced reactivities owing to their intrinsic lower reactivity (products **3p–r**). It was most exciting that the present protocol for the catalytic hydrophosphonyla-

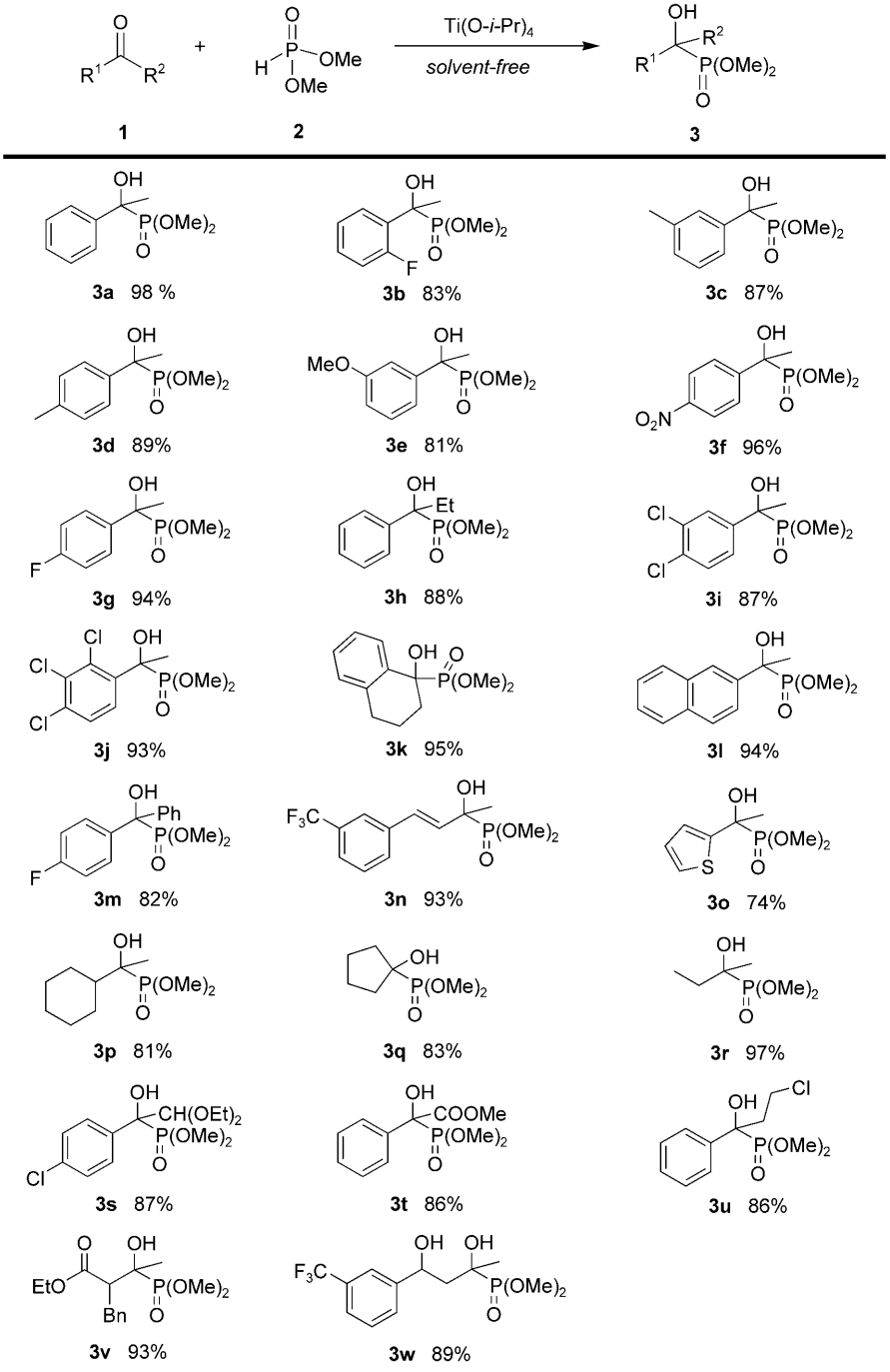
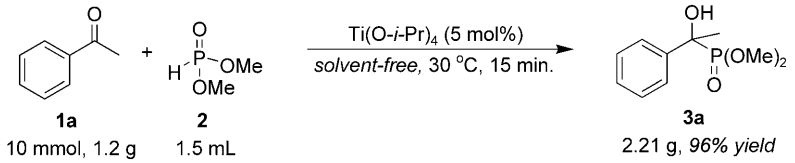
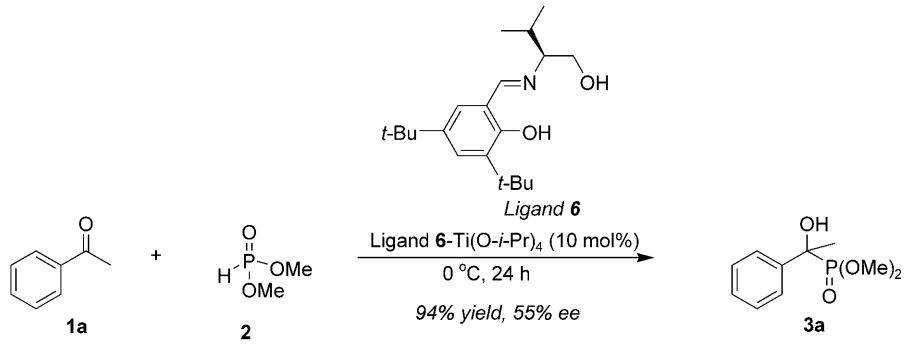


Figure 2. Substrate scope for the catalytic hydrophosphonylation of ketones.[16b,17]



Scheme 2. Scaled-up version of the hydrophosphonylation of acetophenone.



Scheme 3. Catalytic asymmetric hydrophosphonylation of acetophenone.

tion of ketones was highly tolerable for functional ketones (products **3t–v**). In particular, the mild acidity of Ti(O-*i*-Pr)$_4$ made it an effective catalyst for the reaction of ketone **1s**, which contained an acid-sensitive functional goup [CH(OEt)$_2$]. The ethyl acetoacetate derivative **1v**, which reacted sluggishly or did not react with dimethyl phosphite under basic conditions owing to the enolization, was also proved to be an excellent substrate for the reaction. Moreover, the β-hydroxy ketone **1w** underwent the hydrophosphonylation smoothly, giving the quaternary 1,3-dihydroxy phosphonate **3w** with 89% yield. It should be mentioned that the current strategy completely avoided the retro-aldol reaction which rapidly proceeds under strong basic conditions.

To test the synthetic potential of the present approach, a large-scale synthesis of quaternary α-hydroxy phosphonate was performed (Scheme 2). By treatment of 10 mmol of acetophenone under the optimal reaction conditions, the desired product was produced with 96% yield within 15 min.

Based on the observations above, a preliminary investigation on the catalytic asymmetric version was performed (Scheme 3). The tridentate Schiff base **6**-Ti(O-*i*-Pr)$_4$ complex catalyzed the asymmetric hydrophosphonylation of acetophenone smoothly under neat conditions, giving the corresponding quaternary α-hydroxy phosphonate in high yield with 55% *ee*.[15e] Although the enantioselectivity was moderate, it should be noted that this is the first example of the catalytic asymmetric hydrophosphonylation of an unactivated ketone.

In conclusion, we have demonstrated the first highly efficient, Lewis acid-catalyzed hydrophosphonylation of ketones. Significant progress has been obtained with an extremely broad substrate scope, giving the corresponding quaternary α-hydroxy phosphonates with high yields. Particularly, the present method showed a good tolerance of functionalized ketones. Moreover, the first catalytic asymmetric hydrophosphonylation of unactivated ketones has also been developed by using a tridentate Schiff base-Ti(O-*i*-Pr)$_4$ complex as the catalyst. Further studies on the mechanism of the reaction as well as the asymmetric synthesis of quaternary α-hydroxy phosphonates are in progress.

Experimental Section

All reactions were carried out under an atmosphere of nitrogen in dry glassware with magnetic stirring. Ketone (0.5 mmol) and dimethyl phosphite (75–200 μL) were added to a dry flask, then Ti(O-*i*-Pr)$_4$ was added under a nitrogen atmosphere. The reaction mixture was stirred at 30 °C or 60 °C. When the reaction was completed, the product was directly purified by column chromatography on silica gel (ethyl acetate/petroleum ether 1:1-ethyl acetate).

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[15] a) It was suspected that the great difference on the reactivity of the reaction for different Lewis acids was mostly dependent on the possible phosphonate-phosphite equilibrium; The Lewis acid activates both the dimethyl phosphite and ketone, while the activation of dimethyl phosphite is more important for the hydrophosphonylation of ketone in this paper. Although the precise order of different Lewis acids for the activation of dimethyl phosphite was hard to determine owing to the difficult observation of the metallo-phosphite, it was believed that basic counterions and a suitable acidity of the Lewis acid were beneficical for the activation of dimethyl phosphite. b) Elevating the reaction temperature was beneficial for the hydrophosphonylation of ketone. c) When the reaction was performed under neat conditions at 60 °C, the reaction could be completed within 45 min using 2.5 mol% $Ti(O\text{-}i\text{-}Pr)_4$. d) Such a highly substrate concentration-dependent hydrophosphonylation of ketones was only observed using $Ti(O\text{-}i\text{-}Pr)_4$ as the catalyst. The yields had no obvious improvement using other Lewis acids under neat conditions.

e) Using 4-methoxybenzoic acid as the additive, the enantioselectivity of the reaction could be further increased to 65% *ee* albeit with a reduced reactivity.

[16] a) Reactions were carried out with **1a** (0.5 mmol), **2** (100 μL) and Ti(O-*i*-Pr)$_4$ (5 mol%) in toluene at 30 °C. b) See Experimental Section.

[17] a) Half of the products were unknown previously, and only six products were reported to be prepared *via* hydrophosphonylation of ketones with moderate to good yields. The quaternary α-hydroxy phosphonates are easily hydrolyzed to the corresponding phosphonic acids, see: b) R. K. M. Burley, S. L. Bearne, *Bioorg. Med. Chem. Lett.* **2005**, *15* 4342; c) L. Yan, J. J. Hale, C. L. Lynch, R. Budhu, A. Gentry, S. G. Mills, R. Hajdu, C. A. Keohane, M. J. Rosenbach, J. A. Milligan, G.-J. Shei, G. Chrebet, J. Bergstrom, D. Card, H. Rosen, S. M. Mandala, *Bioorg. Med. Chem. Lett.* **2004**, *14* 4861; d) S. Chen, C. Yuan, *Synthesis* **1993**, 1074.

