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Formation of α-hydroxyketones via irregular Wittig reaction

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ABSTRACT

Addition reactions of (1-methoxyalkyl)triphenylphosphonium ylides, derived from the corresponding Wittig salts and *n*-BuLi, to aldehydes were investigated. It was revealed that the betaine LiX complexes, the primary adducts, were converted to α-hydroxyketones, prior to the formation of oxaphosphetanes, by addition of aqueous NH_4Cl at low temperature.

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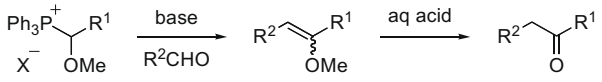
The Wittig reaction[1] is widely applied in organic synthesis because of its high reliability. Its excellent chemoselectivity and few side reactions make it attractive for the syntheses of highly functionalized natural products. Among the many types of Wittig reagents, (1-methoxyalkyl)triphenylphosphonium ylides, derived from the corresponding Wittig salts and a base, are useful reagents because elongated ketones are obtained after acid hydrolysis of the adducts, enol ethers (Scheme 1).[2]

We have recently investigated this type of Wittig reaction using the ylide derived from (1-methoxyalkyl)triphenylphosphonium salt **1** and the substituted benzaldehyde **2** (Table 1). To a THF solution of salt **1** was added *n*-BuLi in hexane at −40 °C. To the resulting red ylide solution was added aldehyde **2** in THF at the same temperature. After the addition of **2** and stirring for 10 min, the reaction temperature was raised to rt during a period of 15 min, and the mixture was quenched with saturated aqueous NH_4Cl. As a result, the desired enol ether **3** and the unexpected α-hydroxyketone **4** were obtained in 72% and 19% yields, respectively (entry 1). When the addition of aldehyde **2** was carried out at −78 °C, the yield of α-hydroxyketone **4** increased to 30% (entry 2). Interestingly, α-hydroxyketone **4** became the major adduct (81% yield), when the reaction was quenched at −78 °C (entry 3).

There are three precedents that give α-hydroxyketones or esters via the Wittig-type reactions (Scheme 2). Diethyl 1-(trimethylsiloxy)-1-phenylmethylphosphonate anion added to aldehydes or ketones, followed by a silyl migration and elimination of diethyl lithium phosphite, provided α-hydroxyketones (Scheme 2a).[3] (Dimethoxymethyl)diphenylphosphine oxide anion reacted with aldehydes, and the resulting adducts were transformed into α-hydroxyesters after acid workup, concomitant with elimination of diphenylphosphine oxide (Scheme 2b).[4] Addition of (1-alkoxyalkyl)triphenylphosphonium ylides, the same type as our ylide, to aldehydes afforded α-alkoxyketones via simultaneous hydride shift and triphenylphosphine elimination (Scheme 2c).[5] In this case, however, the reaction and workup conditions were quite different from those of our case, and the alkoxy and keto functions were interchanged. To the best of our knowledge, formation of α-hydroxyketones in the course of the Wittig reaction using (1-methoxyalkyl)triphenylphosphonium ylides has never been reported. This extraordinary product formation prompted us to explore the utility and mechanism of such an irregular Wittig reaction.

We first examined this coupling using the known (1-methoxyhexyl)triphenylphosphonium salt **5a**[6] and benzaldehyde (**6**) (Table 2). Since the normal Wittig reaction product, the enol ether, was unstable under the workup conditions (saturated aqueous NH_4Cl), the isolated product was the corresponding ketone **7a**.[7] When the coupling reaction was carried out at −40 °C or −78 °C and the quenching was conducted at the same temperature, α-hydroxyketone **8a**[8] was almost exclusively obtained (entries 1 and 3). However, when the reaction temperature was raised to rt



Scheme 1. Wittig reaction of (1-methoxyalkyl)triphenylphosphonium ylides with aldehydes.

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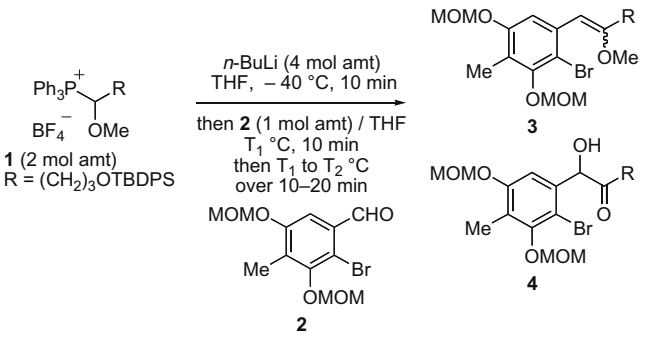
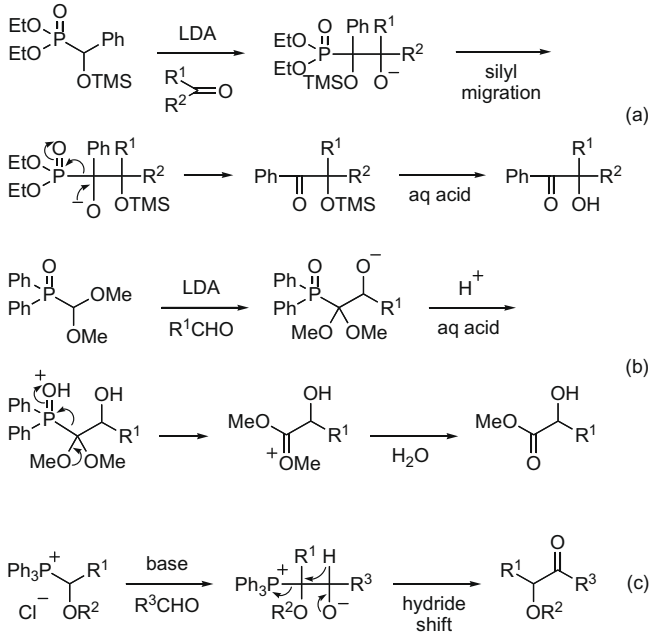
Table 1
Addition of (1-methoxyalkyl)triphenylphosphonium ylide to the substituted benzaldehyde **2**



Entry	T_1 (°C)	T_2 (°C)	Yield (%)	
			3	**4**
1[a]	−40	rt	72[c]	19
2[a]	−78	rt	48[c]	30
3[b]	−78	−78	8[c]	81

[a] After the addition of **2** and stirring for 10 min, the temperature was raised to rt during a period of 15–20 min, and the mixture was quenched with saturated aqueous NH_4Cl.
[b] After the addition of **2** and stirring for 20 min, the mixture was quenched with saturated aqueous NH_4Cl at the same temperature.
[c] *Z*/*E* = 1.4:1 (entry 1), 2.2:1 (entry 2), and 9:1 (entry 3).

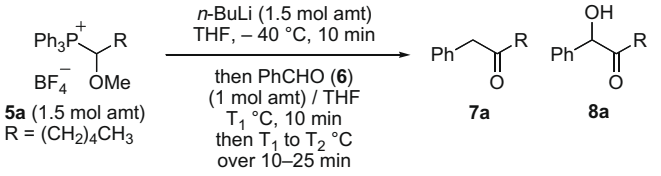


Scheme 2. Three precedents giving α-hydroxyketones or esters via Wittig-type reactions.

before quenching, the normal Wittig product **7a** became the major product (entries 2 and 4).

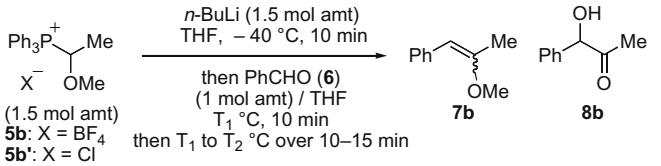
We next used (1-methoxyethyl)triphenylphosphonium salts **5b**[9] (X = BF_4) and **5b′**[2] (X = Cl) (Table 3). Under the low-temperature quenching conditions, α-hydroxyketone **8b**[10] was obtained in good yield (entries 1 and 3). No **7b**[11] was detected by ^1H NMR analysis of the crude products. In contrast to the cases in Table 2,

Table 2
Addition of (1-methoxyhexyl)triphenylphosphonium ylide to benzaldehyde (**6**)



Entry	T_1 (°C)	T_2 (°C)	Yield (%)	
			7a	**8a**
1	−40	−40	3	93
2	−40	rt	72	19
3	−78	−78	Trace	73
4	−78	rt	70	19

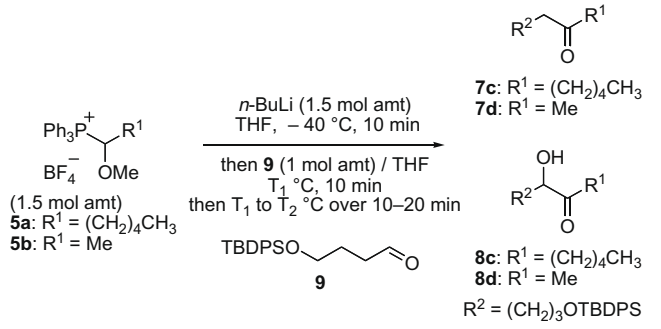
Table 3
Addition of (1-methoxyethyl)triphenylphosphonium ylide to benzaldehyde (**6**)



Entry	Salt	T_1 (°C)	T_2 (°C)	Ratio **7b**:**8b**[a]	Yield (%) of **8b**
1	**5b**	−78	−78	<1:>99	89
2	**5b**	−40	rt	11:89[b]	88
3	**5b′**	−78	−78	<1:>99	75
4	**5b′**	−40	rt	36:64[b]	54

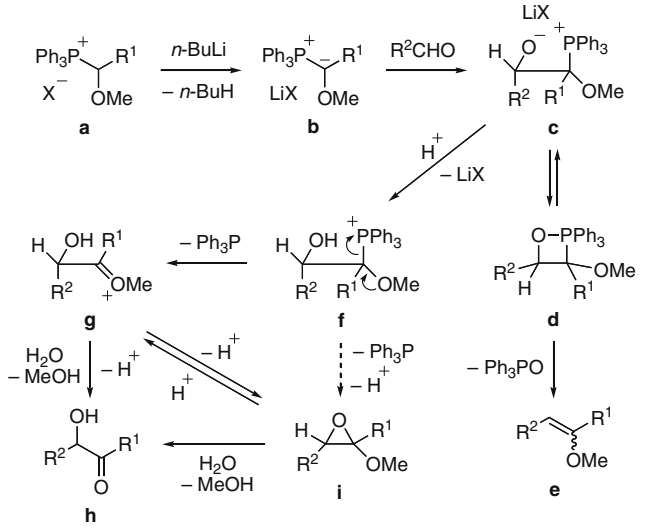
[a] Ratio was determined by ^1H NMR analysis of the crude products.
[b] *Z*/*E* of **7b** = 12:1 (entry 2) and 25:1 (entry 4).

Table 4
Addition of (1-methoxyalkyl)triphenylphosphonium ylide to aldehyde **9**



Entry	Salt	T_1 (°C)	T_2 (°C)	Yield (%)	
				7	**8**
1	**5a**	−78	−78	0	83
2	**5a**	−40	rt	63	5
3	**5b**	−78	−78	0	84
4	**5b**	−40	rt	44	43

α-hydroxyketone **8b** was the major product even though the temperature was raised to rt before quenching (entries 2 and 4). The reasons behind both the variable behavior with alkyl-chain length (pentyl in Table 2 and methyl in Table 3) and the selectivity difference that depends on the counteranions (BF_4 and Cl in entries 2 and 4 in Table 3) remain obscure.



Scheme 3. Plausible mechanism of the irregular Wittig reaction.

The application of this addition reaction to aliphatic aldehyde **9**[12] was also investigated (Table 4). To the ylide, derived from **5a** or **5b**, was added aldehyde **9** at −78 °C, and the mixture was quenched with saturated aqueous NH_4Cl at −78 °C, affording only the corresponding α-hydroxyketone, **8c** or **8d**, in good yield (entry 1 or 3). On the other hand, the normal Wittig reaction predominantly proceeded (63% yield of **7c**, entry 2) or a 1:1 mixture of **7d**[13] and **8d** was obtained (entry 4) when the reaction temperature was raised to rt.

In order to obtain some insight on the mechanism of this irregular Wittig reaction, we examined the effect of intramolecular lithium chelation between the alkoxide and methoxy groups in the betaine LiX complex (**c** in Scheme 3, vide infra). This chelation might prevent the formation of the oxaphosphetane at low temperature. Along these lines, the trapping reagent (12-crown-4 ether, HMPA, or TMEDA) was added to the ylide solution of **5a** at −40 °C before addition of benzaldehyde (**6**) at −78 °C. The result remained unchanged compared to entry 3 in Table 2.

All these experimental results show that quenching the reaction mixture of the Wittig ylide and the aldehyde used in this study with aqueous NH_4Cl at low temperature affords the α-hydroxyketone as the major or exclusive product. A plausible mechanism of this irregular Wittig reaction would be as follows (Scheme 3). Wittig ylide **b**, derived from Wittig salt **a** and *n*-BuLi, adds to the aldehyde to afford the betaine LiX complex **c**.[14] According to the normal Wittig course, **c** affords enol ether **e** through oxaphosphetane **d**. In contrast, addition of aqueous NH_4Cl to the reaction mixture at low temperature leads to **f**, from which elimination of triphenylphosphine occurs[15] which is assisted by the methoxy group. The resulting oxonium intermediate **g** is hydrolyzed to α-hydroxyketone **h**. The alternative mechanism involving oxirane formation from **f** to **i** might be unlikely according to the computational calculations[16] that show oxirane formation from the betaine intermediate (nucleophilic displacement of the phosphine) involves a very significant barrier.[17] However, we do not discard methoxyoxirane **i** that is available from oxonium intermediate **g** as a possible intermediate.[18]

In summary, we revealed that additions of some (1-methoxyalkyl)triphenylphosphonium ylides to aldehydes at −78 °C followed by quenching the reaction mixture with aqueous NH_4Cl at −78 °C afforded α-hydroxyketones.[19] This is the first example of phosphonium ylides acting as an acyl anion equivalent. The irregular Wittig reactions described here are an alternative to 2-lithio-1,3-dithiane reactions[20] with aldehydes.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.102.

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18. Methoxyoxirane **i** has not been detected in the reaction mixture.
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