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COMMUNICATION

An unusual reaction of α-alkoxyphosphonium salts with Grignard reagents under an O_2 atmosphere†

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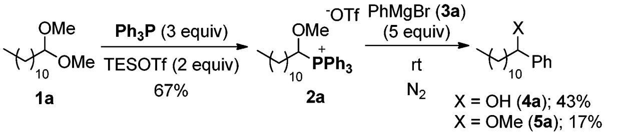
An unusual and novel reaction of α-alkoxyphosphonium salts, generated from *O*,*O*-acetals and Ph_3P, with Grignard reagents under an O_2 atmosphere afforded alcohols in moderate to high yields. It was clarified by isotopic labelling experiments that the reaction proceeded *via* a novel radical pathway.

The α-alkoxyphosphonium salts are good precursors of vinyl ethers for Wittig reactions, of which there are numerous applications in the total synthesis of natural products.[1] Despite the utility of α-alkoxyphosphonium salts in organic synthesis, α-alkoxyphosphonium salts are seldom used for other reactions. Only a few groups have reported the nucleophilic substitution reaction of α-alkoxyphosphonium salts,[2] but this reaction has not been fully investigated.

Recently, as a part of our studies about the reactivities of cationic intermediates,[3] we have developed the efficient substitution reactions of the α-alkoxyphosphonium salts with various nucleophiles.[4] The α-alkoxyphosphonium salts prepared from *O*,*O*-acetals and tris(*o*-tolyl)phosphine [$(o\text{-tol})_3P$] are reactive to nucleophiles such as H_2O, cyanides, thiols, and Grignard reagents, *via* the elimination of $(o\text{-tol})_3P$. The progress of these substitution reactions depends on the type of phosphine. For example, when we used triphenylphosphine (Ph_3P) as the phosphine source, the substitution reaction of the α-methoxyphosphonium salt **2a**, which was obtained in 67% yield by the reaction of dimethyl acetal **1a** and Ph_3P, with H_2O did not effectively proceed.[5] However, when PhMgBr (**3a**) was used as a nucleophile for the substitution reaction of **2a**, we encountered an unexpected phenomenon (Scheme 1). The reaction of **2a** with an excess amount of **3a** afforded the alcohol **4a** (43%) as the major product along with the substituted product **5a** (17%). To the best of our knowledge, such a reaction has never been reported. We now report a novel reaction of α-alkoxyphosphonium salts with Grignard reagents and its mechanistic study.

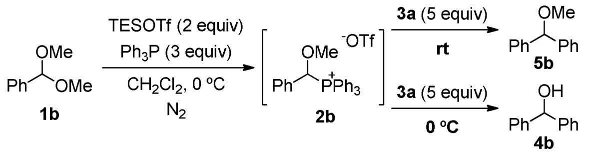


Scheme 1 An unusual reaction of the α-methoxyphosphonium salt with PhMgBr.

For the purpose of revealing the scope and limitation of this unusual reaction, we chose the α-methoxyphosphonium salt **2b** as the starting material, which was generated *in situ* from benzaldehyde dimethyl acetal **1b** because the α-alkoxyphosphonium salts are usually highly polar compounds and not easily handled. The α-alkoxyphosphonium salt **2b** formed from **1b** and Ph_3P *in situ* was treated with 5 equivalents of **3a** under a N_2 atmosphere. The major product was altered by the reaction temperature. That is, the benzhydrol methyl ether **5b** was obtained as a major product when the reaction was conducted at room temperature, but benzhydrol **4b** was the major product at 0 °C (Scheme 2).

It was curious that although we repeatedly performed the same reaction at 0 °C, **4b** was obtained in different yields in each run (30–65%). We could not initially understand why the reaction afforded such varying results. Since phenol (PhOH) and triphenylphosphine oxide ($Ph_3P{=}O$) were obtained as by-products, we then presumed that the N_2 gas contained a small amount of O_2 gas,[6] which promoted this reaction as well as oxidized PhMgBr[7] and Ph_3P to form these by-products. The varying results must be due to an inconsistent ratio of O_2 gas in the N_2 gas.

Based on this hypothesis, we carried out the reaction at 0 °C under an O_2 atmosphere. Consequently, **4b** was obtained in a reproducible yield (entry 1, Table 1), and no reaction proceeded under an argon atmosphere (entry 2). Therefore, the existence of O_2 is essential for the reaction. Dry air was



Scheme 2 Preliminary experiments with the aromatic α-methoxyphosphonium salt.

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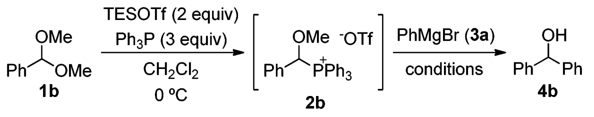
Table 1 Optimization of the reaction conditions[a]



Entry	Equiv. of **3a**	Conditions	Yield (%)
1	5	O_2/0 °C	40
2	5	Ar/0 °C	ND[b]
3	5	Dry air/0 °C	81
4	5	Dry air/−40 °C	57
5	1	Dry air/0 °C	Trace
6	3	Dry air/0 °C	49

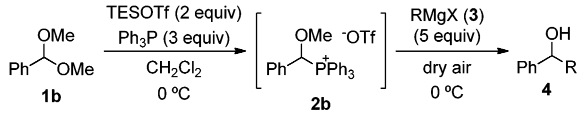
[a] Reaction conditions: to a solution of **1b** (1 equiv.) in CH_2Cl_2 (0.2 mol L^{-1}) under O_2, Ar or dry air, Ph_3P (3 equiv.) and TESOTf (2 equiv.) were added at 0 °C, and the mixture was stirred for 0.5 h. Then, **3a** was added, and the solution was stirred for 2–4 h. [b] Not detected.

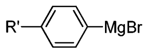
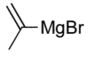
suitable for this reaction as the O_2 source (entry 3). When the reaction was performed at a lower temperature (−40 °C), the reaction time was prolonged and no improvement in the yield was observed (entry 4). The use of 1 or 3 equivalents of **3a** decreased the yields of **4b** (entries 5 and 6).

We then examined the reaction with various Grignard reagents under the optimal conditions (Table 2). Various aromatic Grignard reagents with electron-donating or electron-withdrawing groups **3a–d** reacted with the α-methoxyphosphonium salt **2b** under dry air at 0 °C to afford the benzhydrol derivatives **4b–e** (entries 1–4). On the other hand, the alkenyl and alkyl Grignard reagents **3e** and **3f** were not effective in this reaction (entries 5 and 6).

Various α-alkoxyphosphonium salts generated from the *O*,*O*-acetals underwent this reaction (Table 3). Aromatic and heteroaromatic α-alkoxyphosphonium salts derived from the *O*,*O*-acetals **1c–g** were converted into the corresponding diarylmethanols **4c,d,h–j** in good yields (entries 1–5). Cyclic acetal **1h** and diisopropyl acetal **1i** were also transformed into benzhydrol **4b** in good yields (entries 6 and 7). In addition, aliphatic α-alkoxyphosphonium salts derived from the *O*,*O*-acetals **1a,j–m** also reacted with **3a** to give the corresponding alcohols **4a,k–n** in moderate to good yields (entries 8–12). In some cases, the desired reaction proceeded at −40 °C, while the reaction competed with nucleophilic substitution at 0 °C.

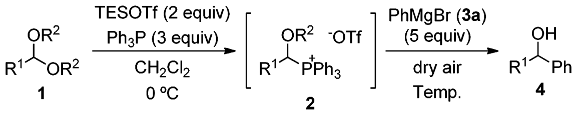
Table 2 Various Grignard reagents[a]

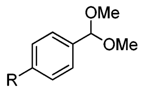
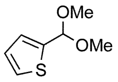
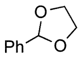
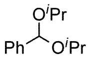
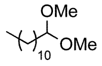
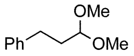
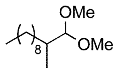
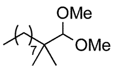
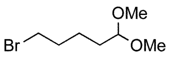


Entry	RMgX	Product	Yield (%)
			
1	R′ = H (**3a**)	**4b**	81
2	R′ = Me (**3b**)	**4c**	86
3	R′ = OMe (**3c**)	**4d**	62
4	R′ = F (**3d**)	**4e**	57
5	 (**3e**)	**4f**	Trace
6	EtMgBr (**3f**)	**4g**	ND[b]

[a] Reaction conditions: to a solution of **1b** (1 equiv.) in CH_2Cl_2 (0.2 mol L^{-1}) under dry air, Ph_3P (3 equiv.) and TESOTf (2 equiv.) were added at 0 °C, and the mixture was stirred for 0.5 h. Then, **3** (5 equiv.) was added, and the solution was stirred for 2–4 h at 0 °C. [b] Not detected.

Table 3 The reaction of various α-alkoxyphosphonium salts with PhMgBr under an O_2 atmosphere[a]

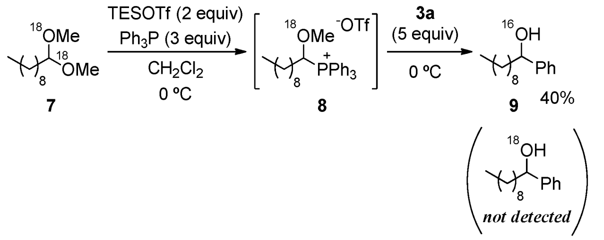


Entry	Substrate	Product	Temp./°C	Yield (%)
				
1	R = Me (**1c**)	**4c**	0	81
2	R = OMe (**1d**)	**4d**	−40	83
3	R = Br (**1e**)	**4h**	0	78
4[b,c]	R = CF_3 (**1f**)	**4i**	−40	63
5	 (**1g**)	**4j**	−40	66
6	 (**1h**)	**4b**	0	83
7[c]	 (**1i**)	**4b**	−40	60
8	 (**1a**)	**4a**	0	56
9	 (**1j**)	**4k**	0	55
10	 (**1k**)	**4l**	0	70
11[c]	 (**1l**)	**4m**	−40	56
12	 (**1m**)	**4n**	0	63

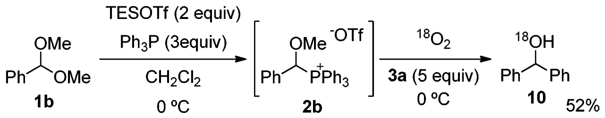
[a] Reaction conditions: to a solution of **1** (1 equiv.) in CH_2Cl_2 (0.2 mol L^{-1}) under dry air, Ph_3P (3 equiv.) and TESOTf (2 equiv.) were added at 0 °C, and the mixture was stirred for 0.5 h. Then, **3a** (5 equiv.) was added, and the solution was stirred for 2–4 h at 0 °C. [b] The reaction of **1f** with Ph_3P and TESOTf was performed at rt. [c] TMSOTf was used instead of TESOTf.

The mechanism of this unusual reaction was then studied. We first synthesized the ^{18}O-labelled dimethyl acetal **7** from *n*-decanal and $CH_3{}^{18}OH$ and carried out the reaction using this labelled acetal. However the ^{18}O atom was not included in the product **9** (Scheme 3).[8]

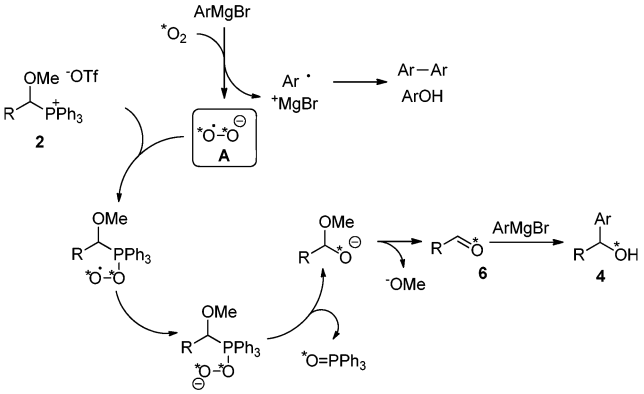
Taking into consideration that O_2 promoted this reaction, the reaction using $^{18}O_2$ gas was then carried out (Scheme 4). It was found that the isotopic oxygen atom was introduced into the product **10** verifying that the O atom was derived from the O_2 gas.



Scheme 3 Isotopic labelling experiment using the ^{18}O-labelled dimethyl acetal **7**.



Scheme 4 Isotopic labelling experiment using an $^{18}O_2$ gas.



Scheme 5 Plausible reaction mechanism.

Based on these results, a novel radical pathway was theorized as depicted in Scheme 5.

A part of the aryl Grignard reagent reacts with O_2, then the superoxide radical anion **A** and the aryl radical are generated.[9] The radical anion species **A** has a high nucleophilicity,[10] and attacks the cationic phosphorus atom of the α-methoxyphosphonium salt **2** leading to the oxidative elimination of the phosphine-like oxaphosphetanes during the Wittig reaction. As soon as the aldehyde **6** is produced, the remaining Grignard reagent reacts with **6** to afford the alcohol **4**. Since the aliphatic Grignard reagents are more reactive to O_2 than aromatic ones,[7c] all of the Grignard reagents seemed to be consumed before reacting with the aldehyde resulting in a trace amount of alcohols **4** (entries 5 and 6, Table 2).

This mechanism was supported by some experiments. First, the addition of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) interrupted the reaction, which indicated that the reaction proceeded *via* a radical pathway. Second, triphenylphosphine oxide was generated in the reaction, suggesting that the α-alkoxyphosphonium salts react with O_2-derived radical species, resulting in the oxidative elimination of phosphine.

In conclusion, we have investigated an unusual and novel reaction of α-alkoxyphosphonium salts with aryl Grignard reagents in the presence of O_2. Various α-alkoxyphosphonium salts and aryl Grignard reagents underwent this reaction to produce the corresponding alcohols. Furthermore, this reaction is suggested to proceed *via* a novel radical pathway. These results open a new aspect of the reactivity of α-alkoxyphosphonium salts.

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Notes and references

1 For recent applications in total synthesis, see: (*a*) W. T. Lambert and S. D. Burke, *Org. Lett.*, 2003, **5**, 515; (*b*) G. A. Molander, K. M. George and L. G. Monovich, *J. Org. Chem.*, 2003, **68**, 9533; (*c*) E. Quéron and R. Lett, *Tetrahedron Lett.*, 2004, **45**, 4527; (*d*) W. T. Lambert, G. H. Hanson, F. Benayoud and S. D. Burke, *J. Org. Chem.*, 2005, **70**, 9382; (*e*) M. E. Jung, J. Cordova and M. Murakami, *Org. Lett.*, 2009, **11**, 3882; (*f*) M. T. Crimmins, M. C. Mans and A. D. Rodríguez, *Org. Lett.*, 2010, **12**, 5028.

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4 H. Fujioka, A. Goto, K. Otake, O. Kubo, K. Yahata, Y. Sawama and T. Maegawa, *Chem. Commun.*, 2010, **46**, 3976.

5 The α-methoxyphosphonium salt **2a** was less reactive to H_2O, so **2a** was able to be easily isolated. See ESI† for details.

6 We used N_2 gas from a nitrogen tank *via* the N_2 gas line. A small amount of O_2 in the air may be present in the N_2 gas line.

7 (*a*) C. W. Porter and C. Steel, *J. Am. Chem. Soc.*, 1920, **42**, 2650; (*b*) H. Gilman and A. Wood, *J. Am. Chem. Soc.*, 1926, **48**, 806; (*c*) M. T. Goebel and C. S. Marvel, *J. Am. Chem. Soc.*, 1933, **55**, 1693; (*d*) M. S. Kharasch and W. B. Reynolds, *J. Am. Chem. Soc.*, 1943, **65**, 501; (*e*) C. Walling and S. A. Buckler, *J. Am. Chem. Soc.*, 1955, **77**, 6032; (*f*) J. F. Garst, C. D. Smith and A. C. Farrar, *J. Am. Chem. Soc.*, 1972, **94**, 7707. For a review, see: (*g*) G. Sosnovsky and J. H. Brown, *Chem. Rev.*, 1966, **66**, 529.

8 See ESI† for details.

9 The reaction of O_2 and Grignard reagents is known to produce radical anion species. See: C. Walling and A. Cioffari, *J. Am. Chem. Soc.*, 1970, **92**, 6609. The aryl radical species coupled to itself to afford a biaryl compound which wasdetected as a by-product.

10 (*a*) E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida and C. S. Shiner, *Tetrahedron Lett.*, 1975, **16**, 3183; (*b*) D. T. Sawyer and J. S. Valentine, *Acc. Chem. Res.*, 1981, **14**, 393, and references cited therein.