A novel and efficient method for the olefination of carbonyl compounds with Grignard reagents in the presence of diethyl phosphite†

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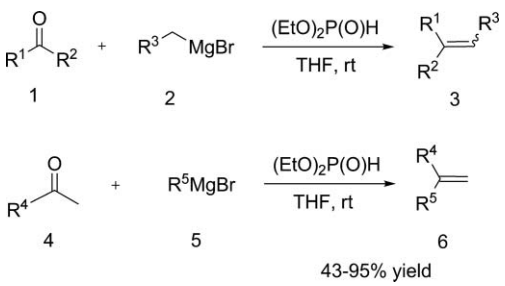
The widely available carbonyl compounds react with Grignard reagents in the presence of diethyl phosphite to give the corresponding olefins in good to excellent yields: A range of conjugated dienes, terminal olefins, multisubstituted-alkenes and conjugated enynes could be readily obtained by the method in mild conditions.

The carbonyl olefination by the Wittig reaction,[1] Julia–Lythgoe olefination and Peterson olefination,[2] as well as their variants, have become invaluable methods in organic synthesis.[3] However, these reactions could not avoid the need for stepwise generation of ylides under basic conditions. The catalytic alternative to the classic Wittig reaction has proven to be quite promising, avoiding the limitation.[4] Accordingly, several catalytic aldehyde and ketone olefination systems have been reported based on Mo,[5] Re,[6] Fe,[7] Ru,[8] Co,[9] Rh,[10] Cu,[11] and Ir[12] complexes. And these nonbasic reaction conditions allowed the synthesis of conjugated esters and ketones in high yields and excellent *E*-selectivity. However, these reactions based on a variety of ancillary ligands. Olefination of dithioacetals with Grignard reagents was reported by Luh.[13] In this reaction, the substrates-dithioacetals were obtained from carbonyl compounds, and the nickel catalyst was required. Although the carbonyl olefination has been well explored, the attempt to find a one-pot synthesis method of olefin from environment-friendly and inexpensive reagents is meaningful and needed.

Herein, we present our preliminary results, which have led to the development of a new method for the olefination of carbonyl compounds with Grignard reagents in the presence of diethyl phosphite (Scheme 1).



Scheme 1 Olefination of carbonyl compounds with Grignard reagents.

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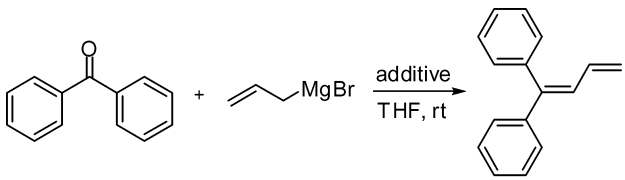
Table 1 Optimization of reaction conditions[a]



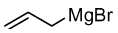
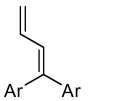
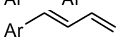
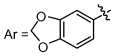
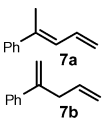
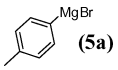
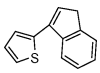
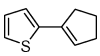
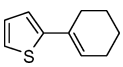
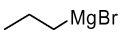
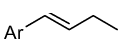
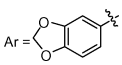
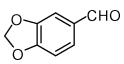
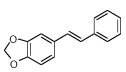
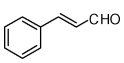
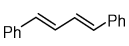
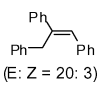
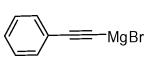
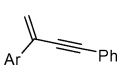
1a 2a 3a

Entry	Additive (equiv.)	**2a** (equiv.)	Time/h	Yield (%)[b]
1	$Ph_2P(O)H$ (1.0)	3	24	None
2	$(EtO)_3P$ (1.0)	3	24	None
3	$(EtO)_2P(O)CH_2COOEt$ (1.0)	3	24	None
4	$(EtO)_3PO$ (1.0)	3	24	None
5	Ph_3P (1.0)	3	24	None
6	$(EtO)_2P(O)H$ (1.0)	3	5	79
7	$(EtO)_2P(O)H$ (0.8)	3	5	65
8	$(EtO)_2P(O)H$ (1.2)	3	5	85
9	$(EtO)_2P(O)H$ (1.5)	3	5	80
10	$(EtO)_2P(O)H$ (1.2)	4	5	67[c]
11	$(EtO)_2P(O)H$ (1.2)	3	5	90[c]
12	$(EtO)_2P(O)H$ (1.2)	2	5	86[c]
13	$(EtO)_2P(O)H$ (1.2)	1	5	32[c]
14	$(i\text{-}PrO)_2P(O)H$(1.2)	3	5	82
15	$(PhO)_2P(O)H$(1.2)	3	24	42

[a] To a solution of **1a** (0.5 mmol) in THF (3 mL) was added **2a** in THF (0.5 M, 3 mL, 1.5 mmol) and additive at room temperature. [b] Isolated yield based on 1a after silica gel chromatography. [c] To a solution of **1a** (0.5 mmol) in THF (3 mL) was added **2a** in THF (0.5 M) at room temperature, and the mixture was stirred for 30 min, then the additive (0.6 mmol) was added to this mixture at room temperature.

In initial experiments, we investigated the effect of different additives on the carbonyl olefination with the model reaction between the benzophenone and allylmagnesium bromide (Table 1). Treatment of benzophenone with allylmagnesium bromide in THF at room temperature in the presence of diphenylphosphine oxide, triethylphosphite, ethyl-2-(diethoxyphosphoryl) acetate, triethylphosphate or triphenylphosphine did not afford the product **3a** (Table 1, entries 1–5). After some investigations, we concluded that the diethyl phosphite was the effective additive, and when the 1.2 equiv. of it was added to the mixture of benzophenone and 2 equiv. of allylmagnesium bromide affording the product **3a** in 86% yield at room temperature (Table 1, entry 12). It is worth mentioning that the use of $(EtO)_2P(O)H$ as the additive is more advantageous than $(i\text{-}PrO)_2P(O)H$ and $(PhO)_2P(O)H$ in terms of cheap and readily available considerations. Encouraged by this efficient experimental results, we examined the scope of carbonyl compounds and Grignard reagents. The representative examples are presented in Table 2.

Table 2 Olefination of carbonyl compounds and Grignard reagents[a]

Entry	Carbonyl Compounds		Grignard Reagents	Product	Yield (%)[b]
1		Ar = C_6H_5			90
2		Ar = 4-ClC_6H_4			83
3		Ar = 4-$MeOC_6H_4$			95
4	Ar–CHO	Ar = 4-$MeOC_6H_4$			82
5					87
6		Ar = 2-furan			70
7			 (7a:7b = 57:43)	83	
8		Ar = C_6H_5(**4a**)	 (**5a**)		91
9		Ar = 4-ClC_6H_4			86
10		Ar = 4-MeC_6H_4			90
11		Ar = 2-naphthyl			81
12		Ar = 2-thiophene			89
13		Ar = 2-furan			61
14		Ar = C_6H_5			92
15		Ar = 4-BrC_6H_4			94
16		Ar = 4-MeC_6H_4			90
17					87
18					91
19					84
20					82
21	Ar–CHO	Ar = 4-$MeOC_6H_4$			90
22					84
23					43
24		Ar = 4-$MeOC_6H_4$			90
25					90
26					81
27				 (E: Z = 20: 3)	70
28		Ar = C_6H_5			72
29		Ar = 4-MeC_6H_4			83

[a] To a solution of carbonyl compounds (0.5 mmol) in THF (3 mL) was added Grignard reagents in THF (0.5 M, 2.2 mL, 1.1 mmol) at room temperature, and the mixture was stirred for 30 min, then the diethyl phosphite (0.6 mmol) was added to this mixture at room temperature. [b] Isolated yield based on carbonyl compounds after silica gel chromatography.

Olefination of ketones or aldehydes (Table 2) were achieved in good to excellent yields at room temperature using 2.2 equiv. of Grignard reagents and 1.2 equiv. of diethyl phosphite in THF. A range of conjugated dienes (Table 2, entries 1–6 and 26), terminal alkenes (Table 2, entries 8–16), multisubstituted-alkenes (Table 2, entries 17–20, 23–24 and 27) and conjugated enynes (Table 2, entries 28 and 29) could be readily obtained by the method in mild conditions.

And we were pleased to find that (*E*)-alkenes could be obtained as the predominant products by the reaction of aldehydes with Grignard reagents in high stereoselectivity (Table 2, entries 4–6, 21–22, 25–26), the corresponding (*Z*)-alkenes were not found from ^{1}HNMR spectrums. However, when 1,2-diphenylethanone reacted with benzylmagnesium bromide, the (*E*)/(*Z*) mixture as product was obtained (Table 2, entry 27). When the reaction of allylmagnesium bromide with acetophenone was investigated, the mixture of conjugated diene (Table 2, entry 7a) and 1,4-diene (Table 2, entry 7b) as product was obtained.

The yields both electron-donating (Table 2, entries 3–5, 10, 16 and 29) and electron-withdrawing groups (Table 2, entries 2, 9 and 15) in benzene rings be employed are good to excellent. Moreover, thiophene and furan heterocycles (Table 2, entries 6, 12–19) participate efficiently in the reaction.

It is worth mentioning that the conjugated enynes were also obtained from this method (Table 2, entries 28 and 29). Compared with the recently-developed methods, namely, metal-catalyzed dimerization/oligomerization of terminal alkynes to afford conjugated enynes,[14] the advantages of this methodology were worth notice.

Aliphatic ketones also reacted with aliphatic and heterocycle Grignard reagents in the presence of diethyl phosphite to give the corresponding alkenes. But, the reaction yield of 2-adamantanone with ethylmagnesium bromide was lower (Table 2, entry 23). And cycloolefins could also be obtained in good to excellent yields (Table 2, entries 17, 18 and 19).

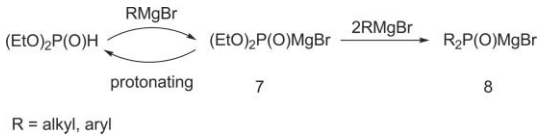
Preliminary studies were undertaken to probe the mechanism for this olefination process. Noticeably, this reaction could not occur in the absence of diethyl phosphite. To investigate the role of diethyl phosphite during this transformation, we tested acids as the additive, the results indicated that no or only trace amounts of products were observed (Table 3, entries 1–3). Thus, it was clear that the method we reported in this communication was quite different from the reaction by the acid-catalyzed dehydration of hydroxide compounds.[15]

Table 3 Acids or alkalis as additive in the reaction[a]

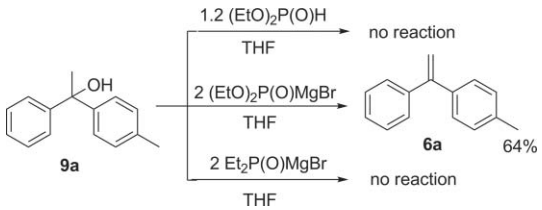
Entry	Substrate	Additive (equiv.)	**5a** (equiv.)	Time/h	Yield (%)[b]
1	**4a**	H_3PO_4(1.2)	3	24	Trace
2	**4a**	$AlCl_3$(1.2)	3	24	None
3	**4a**	CF_3COOH(1.2)	3	24	None
4	**4a**	EtONa(1.2)	2	24	None
5	**4a**	NaH(1.2)	2	24	None
6	**4a**	$(EtO)_2P(O)MgBr$(1.2)	1.2	5	85
7	**4a**	$(EtO)_2P(O)Na$(1.2)	1.2	24	None
8	**9a**	$Et_2P(O)MgBr$(2)	1.2	24	None

[a] To a solution of substrates (0.5 mmol) in THF (3 mL) was added **5a** in THF (0.5 M, 2.2 mL, 1.1 mmol) at room temperature, and the mixture was stirred for 30 min, then the additive (0.6 mmol) was added to this mixture at room temperature. [b] Isolated yield based on substrate after silica gel chromatography.

The reaction of diethyl phosphite with Grignard reagents[16] (Scheme 2) indicate that diethyl phosphite, magnesium bromide diethoxy(oxo)phosphate(III) (**7**) or dialkylphosphinylmagnesium bromide (**8**) may be the accelerant for the olefination. During the course of our studies on mechanism, we found that the most diethyl phosphite could be recovered after the reaction. So, we first exclude the possibility of dialkylphosphinylmagnesium bromide (**8**). We re-investigated this reaction employing the 1-phenyl-1-*p*-tolylethanol (**9a**) as substrate to react with the diethyl phosphite, magnesium bromide diethoxy(oxo)phosphate(III) (**7**) or magnesium bromide diethylphosphinite and found that only **7** give the product in medium yield (Scheme 3). Thus, **7** was proposed as a key intermediate during this transformation. And olefination was achieved in good yield at room temperature employs 1.2 equiv. of **5a** and 1.2 equiv. of **7** in THF (Table 3, entry 6).



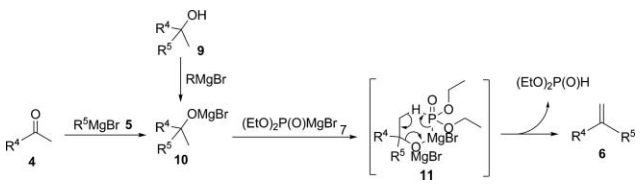
Scheme 2 The reaction of diethyl phosphite with Grignard reagent.



Scheme 3 The reaction of 1-phenyl-1-*p*-tolylethanol with diethyl phosphite, magnesium bromide diethoxy(oxo)phosphate(III) or magnesium bromide diethylphosphinite.

To further understand the mechanism of this transformation, we tested other alkalis instead of **7** as an additive, however, there was no product observed (Table 3, entries 4, 5 and 7). Unfortunately, we can not use a catalytic amount of diethyl phosphite in this reaction because diethyl phosphite was also transformed to **8**, shown in Scheme 2. The **8** could not promote the reaction (Table 3, entry 8).

On the basis of these preliminary results, the mechanism of this transformation was hypothesized as shown in Scheme 4. It was revealed that the six-centered transition state for the olefination reaction **11**, It was the P anion that abstracts the H of the methyl group and the –MgBr of **7** was the assistant.



Scheme 4 Proposed mechanism for olefination of carbonyl.

In summary, we have demonstrated a one-pot manner olefination of carbonyl compounds with Grignard reagents. A

range of conjugated dienes, terminal alkenes, multisubstituted-alkenes and conjugated enynes could be readily obtained in the mild conditions. Further investigation of the usage of other organometal reagents are in progress in our group.

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Notes and references

1 (*a*) A. Maercker, *Org. React.*, 1965, **14**, 270; (*b*) W. C. Still and C. Gennari, *Tetrahedron Lett.*, 1983, **24**, 4405; (*c*) M. J. Peterson and E. Vedejs, *Top. Stereochem.*, 1994, **21**, 1.
2 J. Pospisil, T. Pospisil and I. E. Marko, *Org. Lett.*, 2005, **7**, 2373.
3 M. Lakhrissi and Y. Chapleur, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 750.
4 F. M. Pedro, A. M. Santos, W. Baratta and F. E. Kühn, *Organometallics*, 2007, **26**, 302.
5 X. Y. Lu, H. Fang and Z. J. J. Ni, *J. Organomet. Chem.*, 1989, **373**, 77.
6 (*a*) A. M. Santos, C. C. Romao and F. E. Kuhn, *J. Am. Chem. Soc.*, 2003, **125**, 2414; (*b*) W. A. Herrmann and M. Wang, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1641; (*c*) W. A. Herrmann, P. W. Roesky, M. Wang and W. Scherer, *Organometallics*, 1994, **13**, 4531; (*d*) E. M. Carreira and B. E. Ledford, *Tetrahedron Lett.*, 1997, **38**, 8125; (*e*) X. Y. Zhang and P. Chen, *Chem.–Eur. J.*, 2003, **9**, 1852; (*f*) R. Harrison, A. Mete and L. Wilson, *Tetrahedron Lett.*, 2003, **44**, 6621; (*g*) F. E. Kühn, A. Scherbaum and W. A. Herrmann, *J. Organomet. Chem.*, 2004, **689**, 4149; (*h*) A. M. Santos, F. M. Pedro, A. A. Yogalekar, I. S. Lucas, C. C. Romao and F. E. Kühn, *Chem.–Eur. J.*, 2004, **10**, 6313; (*i*) F. M. Pedro, S. Hirner and F. E. Kühn, *Tetrahedron Lett.*, 2005, **46**, 7777; (*j*) R. M. Hua and J. L. Jiang, *Curr. Org. Synth.*, 2007, **4**, 151.
7 (*a*) G. A. Mirafzal, G. L. Cheng and L. K. Woo, *J. Am. Chem. Soc.*, 2002, **124**, 176; (*b*) V. K. Aggarwal, J. R. Fulton, C. G. Sheldon and J. D. Vicente, *J. Am. Chem. Soc.*, 2003, **125**, 6034; (*c*) Y. Chen, L. Huang, M. A. Ranade and X. P. Zhang, *J. Org. Chem.*, 2003, **68**, 3714; (*d*) Y. Chen, L. Huang and X. P. Zhang, *J. Org. Chem.*, 2003, **68**, 5925; (*e*) Y. Chen, L. Huang and X. P. Zhang, *Org. Lett.*, 2003, **5**, 2493; (*f*) G. L. Cheng, G. A. Mirafzal and L. K. Woo, *Organometallics*, 2003, **22**, 1468; (*g*) V. B. Sharma, S. L. Jain and B. Sain, *Catal. Lett.*, 2004, **98**, 141.
8 (*a*) O. Fujimura and T. Honma, *Tetrahedron Lett.*, 1998, **39**, 625; (*b*) E. Graban and F. R. Lemke, *Organometallics*, 2002, **21**, 3823; (*c*) W. Sun and F. E. Kühn, *Appl. Catal., A*, 2005, **285**, 163; (*d*) W. Sun, B. S. Yu and F. E. Kühn, *Tetrahedron Lett.*, 2006, **47**, 1993; (*e*) F. M. Pedro, A. M. Santos, W. Baratta and F. E. Kühn, *Organometallics*, 2007, **26**, 302.
9 M.-Y. Lee, Y. Chen and X. P. Zhang, *Organometallics*, 2003, **22**, 4905.
10 (*a*) H. Lebel and V. Paquet, *J. Am. Chem. Soc.*, 2004, **126**, 320; (*b*) H. Lebel and V. Paquet, *Org. Lett.*, 2002, **4**, 1671; (*c*) H. Lebel, D. Guay, V. Paquet and K. Huard, *Org. Lett.*, 2004, **6**, 3047; (*d*) H. Lebel, V. Paquet and C. Proulx, *Angew. Chem., Int. Ed.*, 2001, **40**, 2887; (*e*) G. A. Grasa, Z. Moore, K. L. Martin, E. D. Stevens, S. P. Nolan, V. Paquet and H. Lebel, *J. Organomet. Chem.*, 2002, **658**, 126; (*f*) V. Paquet and H. Lebel, *Synthesis*, 2005, 1901.
11 H. Lebel, M. Davi, S. Diez-Gonzalez and S. P. Nolan, *J. Org. Chem.*, 2007, **72**, 144.
12 H. Lebel and C. Ladjel, *Organometallics*, 2008, **27**, 2676.
13 (*a*) T. Y. Luh and D. K. P. Ng, *J. Am. Chem. Soc.*, 1989, **111**, 9119; (*b*) Z. J. Ni, N. W. Mei, X. Shi, Y. L. Tzeng, M. C. Wang and T. Y. Luh, *J. Org. Chem.*, 1991, **56**, 4035; (*c*) W. L. Cheng and T. Y. Luh, *J. Org. Chem.*, 1992, **57**, 3516.
14 (*a*) R. Ghosh, X. W. Zhang, P. Achord, T. J. Emge, K. Krogh-Jespersen and A. S. Goldman, *J. Am. Chem. Soc.*, 2007, **129**, 853; (*b*) B. M. Trost, M. T. Sorum, C. C. Chan and G. Ruehter, *J. Am. Chem. Soc.*, 1997, **119**, 698; (*c*) L. F. Huang, C. W. Chen and T. Y. Luh, *Org. Lett.*, 2007, **9**, 3663; (*d*) A. K. Dash and M. S. Eisen, *Org. Lett.*, 2000, **2**, 737; (*e*) C. L. Yang and S. P. Nolan, *J. Org. Chem.*, 2002, **67**, 591; (*f*) J. H. Lee and K. G. Caulton, *J. Organomet. Chem.*, 2008, **693**, 1664; (*g*) M. Bassetti, C. Pasquini, A. Raneri and D. Rosato, *J. Org. Chem.*, 2007, **72**, 4558; (*h*) J. Ohshita, K. Furumori, A. Matsuguchi and M. Ishikawa, *J. Org. Chem.*, 1990, **55**, 3277; (*i*) S. Pavlik, C. Gemel, C. Slugovc, K. Mereiter, R. Schmid and K. Kirchner, *J. Organomet. Chem.*, 2001, **617–618**, 301; (*j*) K. Melis, D. De. Vos, P. Jacobs and F. Verpoort, *J. Organomet. Chem.*, 2002, **659**, 159; (*k*) X. G. Chen, P. Xue, H. H. Y. Sung, I. D. Williams, M. Peruzzini, C. Bianchini and G. C. Jia, *Organometallics*, 2005, **24**, 4330.
15 J. J. Eisch and G. R. Husk, *J. Org. Chem.*, 1966, **31**, 589.
16 (*a*) O. Gawron, C. Grelecki, W. Reilly and J. Sands, *J. Am. Chem. Soc.*, 1953, **75**, 3591; (*b*) H. R. Hays, *J. Org. Chem.*, 1968, **33**, 3690.