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Phenyldioxaborolane promoted synthesis of bisphosphine compounds

Yin-Wei Sun [a], Peng-Long Zhu [a], Qin Xu [a,*], Min Shi [a,b,*,†]

[a] Key Laboratory for Advanced Materials and Institute of Fine Chemicals, School of Chemistry & Molecular Engineering, East China University of Science and Technology, 130 Mei-Long Road, Shanghai 200237, China
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

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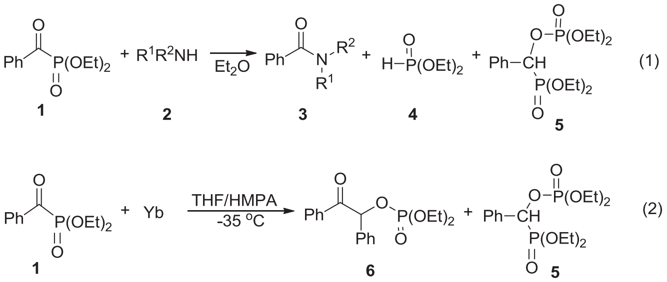
ABSTRACT

Bisphosphine compounds have a wide range of applications. In this paper, we reported that bisphosphine compounds could be prepared in moderate to good yields from dialkyl acylphosphonates under mild conditions in the presence of phenyldioxaborolane and potassium hydroxide via a C–P bond cleavage and a subsequent 1,2-migration of phosphoryl group.

1. Introduction

Organic compounds containing P–C and P–O bonds are not particularly frequent in nature, but, many of them have diverse biological activities and have been widely used in pharmacology.[1] Bisphosphines are important classes of organic compounds, for example, bisphosphonates have been used in the treatment of diseases of bone and calcium metabolism of which osteoporosis was the most common form.[2] More importantly, they can act as inhibitors of proteolytic enzymes, such as rennin,[3] as agents affecting the growth of plants,[4] or as haptens for the development of catalytic antibodies.[5] Besides their valuable applications, the use of them in the production of the dangerous compounds, such as sarin- and soman-type chemical warfare agents must be also noted.[6] Since the last 20 years, many synthetic methods have been developed for the synthesis of these target compounds in a one-pot manner.[2a,7] But these methods usually need harsh reaction conditions, such as at very high temperatures. The synthesis of these compounds under mild conditions is still highly desirable.

Early in 1980, Hata and co-workers have reported that the C–P bond of dialkyl acylphosphonates **1** can be cleaved by amines **2**, affording amides **3** and phosphates **4** in moderate yields (Scheme 1, Eq. 1).[8] In this process a small amount of α-(phosphoryloxy)benzylphosphonates **5** have been isolated. Late, Taniguchi's group found that ethyl benzoylphosphonate **1** can react with Yb metal in THF/hexamethylphosphoramide (HMPA) to produce a mixture of diethyl 1,2-diphenyl-2-oxoethyl phosphate **6** and diethyl l,l-(diethylphosphoryloxy)-l-phenylmethylphosphonate **5** in moderate yields at −35 °C (Scheme 1, Eq. 2).[9] However, these reactions are not very efficient, giving the corresponding diphosphine compounds only in moderate yields via a P–C(OH)–P to P–CH–O–P rearrangement.[10]



Scheme 1. Hata's and Taniguchi's previous work on the preparation of bisphosphines.

Based on these previous reports, we envisaged to use inexpensive reagents to synthesize bisphosphine compounds under mild conditions. Herein, we wish to report the C–P bond cleavage of dialkyl alkenylphosphonates or dialkyl arylallylphosphonates and the subsequent rearrangement in the presence of base and phenyldioxaborolane or phenyl boronic acid to give the corresponding bisphosphine compounds under mild conditions.

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[*] Corresponding authors. E-mail address: mshi@mail.sioc.ac.cn (M. Shi).
[†] Fax: +86 21 64166128.

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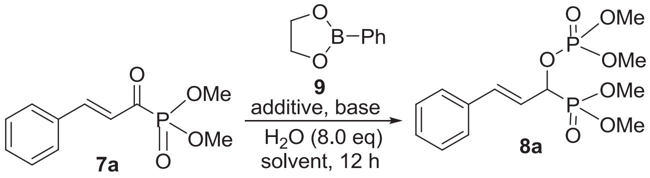
2. Results and discussion

We initially used (*E*)-dimethyl cinnamoylphosphonate **7a** as the substrate in the presence of a weak Lewis acid phenyldioxaborolane **9** and an inorganic base potassium hydroxide (KOH) to examine the reaction outcome and found that (*E*)-1-(dimethoxyphosphoryl)-3-phenylallyl dimethyl phosphate **8a** was formed (Table 1, entry 1). Next, we attempted to optimize the reaction conditions and the results are summarized in Table 1. The diphosphine compound **8a** could be afforded in 87% yield based on two molecules of compound **7a** to generate one product of **8a** in THF in the presence of 2.0 equiv of KOH and 2.0 equiv of **9** (Table 1, entry 4). Reducing the employed amount of KOH or **9** could significantly decrease the yield of **8a** (Table 1, entries 3–6) and the addition of electrophilic reagents, such as benzaldehyde and benzyl alcohol reduced the yield of **8a** (Table 1, entries 1 and 2). The use of strong Lewis acid $Yb(OTf)_3$ gave complex product mixtures (Table 1, entry 7). On the comparison of weak Lewis acids $Si(OEt)_4$, $Al(OH)_3$ or $B(OH)_3$ and $PhB(OH)_2$, the use of 2.0 equiv of boronic acid gave the better results (Table 1, entries 8–13). None of **8a** could be formed either in the absence of a Lewis acid or in the absence of a base (Table 1, entries 14 and 15). The examination of base revealed that KOH is the best one to give **8a** in higher yield (Table 1, entries 16–18). THF is the most suitable solvent for this transformation (Table 1, entries 19–22). We finally determined optimal conditions of the reaction is using 2.0 equiv of 2-phenyl-1,3,2-dioxaborolane **9** as an additive, 2.0 equiv of potassium hydroxide as a base, and carrying out the reaction in THF for 12 h.

Table 1
Optimization of the reaction conditions

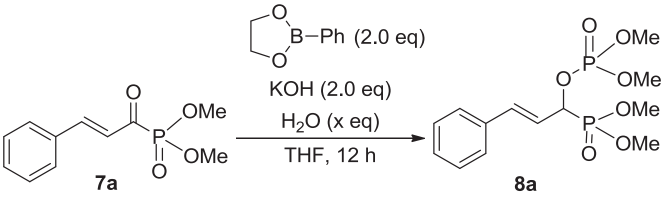


Entry[a]	Additive (equiv)	Base (equiv)	Solvent	Yield (%)[b]
1[c]	**9**[d] (2.0)	KOH (2.0)	THF	54
2[e]	**9** (0.1)	KOH (0.1)	THF	22
3	**9** (0.1)	KOH (0.1)	THF	45
4	**9** (2.0)	KOH (2.0)	THF	87
5	**9** (2.0)	KOH (0.2)	THF	84
6	**9** (0.2)	KOH (2.0)	THF	14
7	$Yb(OTf)_3$ (2.0)	KOH (2.0)	THF	Complex
8	$Si(OEt)_4$ (2.0)	KOH (2.0)	THF	67
9	$Al(OH)_3$ (2.0)	KOH (2.0)	THF	Complex
10	$B(OH)_3$(0.1)	KOH (0.1)	THF	59[f]
11	$B(OH)_3$ (0.5)	KOH (0.5)	THF	67
12[g]	$B(OH)_3$ (2.0)	KOH (2.0)	THF	84
13	$PhB(OH)_2$ (2.0)	KOH (2.0)	THF	86
14	None	KOH (2.0)	THF	Complex
15	**9** (2.0)	None	THF	N.R.
16	**9** (2.0)	K_2CO_3 (2.0)	THF	83
17	**9** (2.0)	Et_3N (2.0)	THF	62
18	**9** (2.0)	DIEA (2.0)	THF	64
19	**9** (2.0)	KOH (2.0)	DCM	72
20	**9** (2.0)	KOH (2.0)	Toluene	53
21	**9** (2.0)	KOH (2.0)	CH_3CN	77
22	**9** (2.0)	KOH (2.0)	Et_2O	52

[a] Reaction was carried out with 0.1 mmol **7a** in 1.0 mL solvent.
[b] Isolate yield based on two molecules of compound **7a** generating one product **8a**.
[c] 1.0 equiv of benzaldehyde was added.
[d] **9** was 2-phenyl-1,3,2-dioxaborolane.
[e] 1.0 equiv of benzyl alcohol was added.
[f] 91% cinnamic acid was observed.
[g] Reaction was carried out within 3 h.

We also found the water has great influence on the yield of **8a**. The influence of water content on the yield of **8a** in this reaction has been shown in Table 2. Adding 8.0 equiv (15 μL) of water in anhydrous THF produced **8a** in 87% yield (Table 2, entry 4). The addition of water >8.0 equiv (15 μL) or <8.0 equiv (15 μL) all decreased the yield of **8a** (Table 2, entries 1–3 and 5–11). When the water content increased to more than 22 equiv (40 μL), the influence of water content on the yield was not obvious (Table 2, entries 8–11).

Table 2
The influence of water on the yield of **8a**

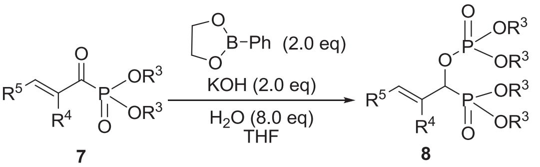


Entry[a]	H_2O (equiv)	Yield of **8a** (%)[b]
1	None	52
2	1.1	50[c]
3	5.6	64
4	8.0	87
5	11	80
6	14	77
7	22	61
8	33	62
9	44	62
10	56	60
11	111	60

[a] Reaction was carried out with 0.1 mmol **7a**, 2.0 equiv 2-phenyl-1,3,2-dioxaborolane and 2.0 equiv KOH in 1.0 mL THF.
[b] Isolate yield based on two molecules of compound **7a** generating one product **8a**.
[c] 61% 2-hydroxyethyl cinnamate **10** was observed (see Supplementary data).

Having identified the optimal conditions, we next examined the substrate generality in the reaction. We found that increasing the steric bulkiness of ester moiety of phosphate group on the substrate decreased the yield of **8** (Table 3, entries 1–3). The

Table 3
Synthesis of bisphosphine compounds **8** with dialkyl acylphosphonates **7** and phenyldioxaborolane



Entry[a]	No.	R^3	R^4	R^5	Yield (%)[b]
					8
1	**7a**	Me	H	C_6H_5	**8a**, 87
2	**7b**	Et	H	C_6H_5	**8b**, 58
3	**7c**	^iPr	H	C_6H_5	**8c**, 47
4	**7d**	Me	Me	C_6H_5	**8d**, 84
5	**7e**	Me	H	*o*-BrC_6H_4	**8e**, 77
6	**7f**	Me	H	*p*-ClC_6H_4	**8f**, 85
7	**7g**	Me	H	*p*-MeC_6H_4	**8g**, 75
8	**7h**	Me	H	*m*-MeC_6H_4	**8h**, 56
9	**7i**	Me	H	*o*-F, *p*-BrC_6H_3	**8i**, 51
10	**7j**	Me	H	*p*-$NO_2C_6H_4$	Complex
11	**7k**	Me	H	*o*-MeO, *p*-BrC_6H_3	**8k**, 83
12	**7l**	Me	H	*m*-$MeOC_6H_4$	**8l**, 73
13	**7m**	Me	H	*p*-$MeOC_6H_4$	Complex
14	**7n**	Me	H	CO	Complex
15	**7o**	Me	H	Me	**8o**, 71

[a] Reaction was carried out with 0.1 mmol **7** in 1.0 mL solvent.
[b] Isolate yield based on two molecules of compound **7** generating one product **8**.