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COMMUNICATION

The C-OH/P-H Dehydrative Cross-Coupling for the Construction of P-C Bond under Metal-free Conditions

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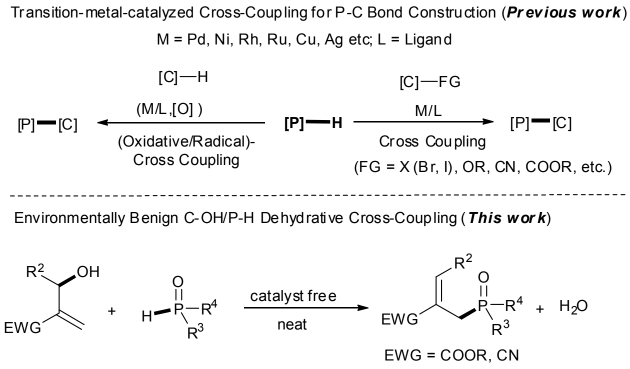
Herein, we report an atom-economical and environmentally benign approach for P-C bond construction via C-OH/P-H dehydrative cross-coupling reaction. This reaction was carried out under metal-free conditions, proceeds in the absence of any solvent and delivered allylic phosphorus compounds in high yields with wide functional group tolerance.

Organophosphorus compounds play important roles in material science, pharmaceuticals and are ubiquitous building blocks or ligands in organic synthesis.[1] Recently, it has also been shown to function as efficient directing group for C-H bond activation.[2] Therefore, the development of convenient and efficient methods for the construction of P-C bond is highly desirable.[1a,3] Since the pioneering work of Hirao in 1981,[4] transition-metal catalyzed cross-coupling reactions of P-H species with organohalides or other counterparts have been established as efficient methods for the construction of P-C bonds.[3c,5] Other methods such as oxidative [6] or radical/radical [7] C-H/P-H cross-coupling and P-H species addition to unsaturated bonds [3,8] are also efficient and direct versions among those reactions (Scheme 1, top). However, the need for strict anhydrous conditions, use of expensive metals, low atom efficiency or/and hazardous conditions besides poor functional group tolerance encourage researchers to continue to search for more practical method for the construction of organophosphorus compounds.[1a,1h,3a] Furthermore, drawbacks associated with quantitative oxidants requirement and strong coordinating character of phosphorus to metal hampering the progress,[6f,6g] impeded the wide application of these methods. Hence, the developments of simple, convenient especially metal-free methods for the construction of P-C bond in a green manner are still highly appealing and essential.



Scheme 1. Cross-coupling strategies for P-C bond formation involving P-H species.

We envisage that the dehydrative coupling of alcohols with phosphorus based reagents as nucleophiles will be an attractive method for the construction of carbon-phosphorus bonds. This is because alcohols are inexpensive and abundantly available. Furthermore, this reaction is atom-economical and environmentally benign since water is the only byproduct (Scheme 1, bottom). Although the dehydrative coupling with many different nucleophiles (NuH) to deliver C-C [9] and C-X [10] (X = N,O,) have been widely studied, the direct dehydrative cross-coupling between C-OH and P-H species remains as an unsolved problem,[11] probably due to the poor leaving ability of hydroxyl group and strong coordinating character of phosphorus to metal.[6] Stimulated by Li's impressive dehydrative coupling between allylic alcohol and terminal alkynes for making C-C bond,[12] we embarked on the development of phosphorylation of allylic alcohol as a novel method for the synthesis of allylic phosphorus compounds, which are extremely valuable synthetic intermediates in pharmaceutical chemistry, agrochemicals, chiral phosphine

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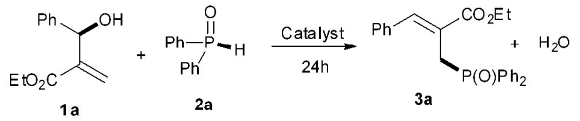
ligands preparation, material chemistry as well as biochemistry. [13] Moreover, the skeleton of 3-phosphono-2-substituted propanates, which are core skeletons of many biologically active compounds,[14] such as Gelatinase A inhibitor,[14a] Enkephalin degrading enzyme inhibitor,[14b] NAALADase inhibitor,[14c] MMP-11 inhibitor,[14d] might be generated from Morita-Baylis-Hillman alcohols and P-H species via C-OH/P-H dehydrative cross-coupling.

In our initial investigation, Morita-Baylis-Hillman (MBH) alcohol **1a** and phosphine oxide **2a** were chosen as the model substrates. $Pd(PPh_3)_4$ (10 mol%) and $Ti(O^iPr)_4$ (30 mol%) were selected as the catalyst system, by which the allylic alcohol **1a** was activated in generating a π-allylpalladium intermediate. Pleasingly, the desired product **3a** was obtained in 85% yield with 89/11 (Z/E) selectivity (Table 1, entry 1). The reaction also could proceed well to give **3a** in moderate yield, when the catalyst palladium was replaced by copper or even in its absence (entries 2,3). That indicated metal is not essential for this dehydrative coupling. Chiral phosphoric acid (4-hydroxydinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide) was then selected as the catalyst, which has been proved as the efficient catalyst in the intramolecular C-O bond formation of allylic alcohol with phenol.[15] In this reaction, **3a** was delivered in 88% yield with high selectivity. To our surprise, in the blank experiment, **3a** could also be detected in 55% yield with excellent selectivity (entry 5). That meant the dehydrative cross-coupling between **1a** and **2a** could proceed in a simple, convenient and environmentally benign manner. In the attempts to improve the yield, several solvents were screened, while no improvement was obtained (For detail see SI). Finally, 85% isolated yield (88% NMR yield) was realized, when the model reaction was conducted without any solvent (entry 6). The reaction could also proceed well at lower temperature with comparative yield (entries 7,8), but higher temperature resulted in diminished yield (entry 9).

Table 1. Optimization of the reaction conditions [a]

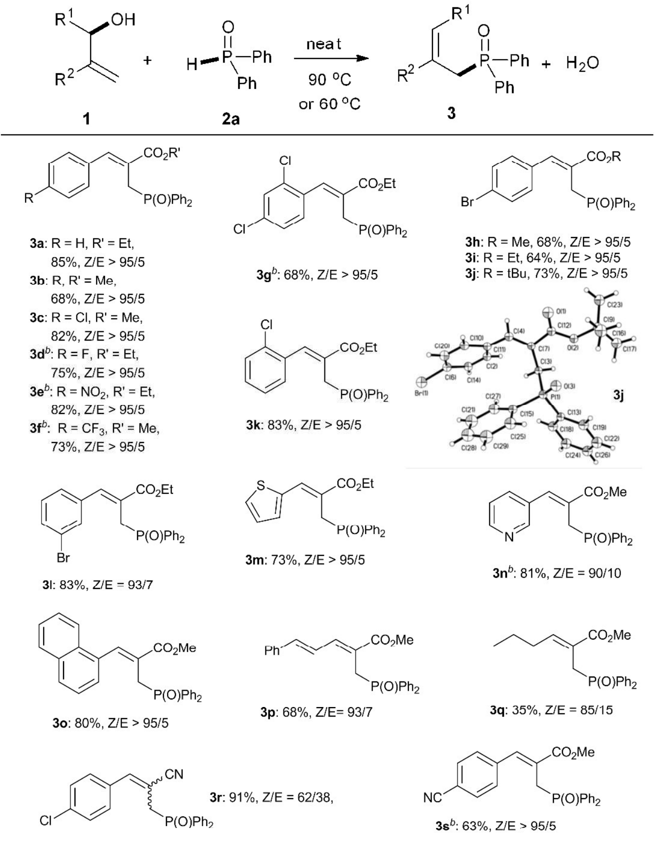


Entry	Cat.(mol%)	Temp. (°C)	Z/E [b]	Yield [c] (%)
1	$Pd(PPh_3)_4$ (10), $Ti(OPr^i)_4$ (30)	90	89/11	85
2	CuI (10), $Ti(OPr^i)_4$ (30)	90	81/19	65
3	$Ti(OPr^i)_4$ (30)	90	79/21	68
4	CPA (30)	90	93/7	88
5	--	90	95/5	55
6 [d]	--	90	>95/5	88 (85)
7 [d]	--	30	>95/5	57
8 [d]	--	60	>95/5	86
9 [d]	--	110	>85/15	34

[a] Experimental conditions see the General method. [b] The ratio of Z/E was determined by ^{31}P NMR of the crude reaction mixture. [c] NMR yields (using mesitylene as internal stand). 1,4-dioxane was selected as the solvent. [d] Without solvent. Value in parentheses is isolated yield.

With the optimized condition established, the substrate scope of allylic alcohol was examined as shown in Table 1. Different allylic alcohols were smoothly transformed into the corresponding allylic phosphorus compounds in good to excellent yields with high to excellent Z/E selectivity. Electronic properties and position of the aryl-substituents on allylic alcohols have limited effect on the yields and selectivity. Among the allylic alcohols examined, the yield and selectivity was insensitive to the steric effect of ester group (**3h-j**). The allylic alcohol with *tert*-butyl ester can provide corresponding product **3j** in high yield with excellent selectivity. The structure of **3j** was also determined by X-ray analysis. [16] Other aromatic group such as thiophen-2-yl (**3m**), pyridin-3-yl (**3n**), and naphthalen-1-yl (**3o**) could also be successfully incorporated in this reaction. Moreover, cinnamoyl was a tolerable group, delivering synthetically useful conjugated 2,4-dienoate skeleton with phosphorus moiety. Alkyl substituted allylic alcohol was tolerated in this reaction albeit with lower yield (**3q**). This is because the MBH alcohols with aromatic group substituents more favored the dehydrate process with the generating larger conjugated system. Cyan substituted allylic alcohol can give **3r** in excellent yield with moderate selectivity. The lower selectivity might attribute to its highly electro-deficient property and reactivity compared with ester group substituted versions. Unfortunately, the formal allylic alcohols such as cinnamyl alcohol or 1-phenylprop-2-en-1-ol cannot deliver the desired products under the identity conditions.

Table 2. Substrate scope of allylic alcohol [a]



3a: R = H, R' = Et, 85%, Z/E > 95/5
3b: R, R' = Me, 68%, Z/E > 95/5
3c: R = Cl, R' = Me, 82%, Z/E > 95/5
3d[b]: R = F, R' = Et, 75%, Z/E > 95/5
3e[b]: R = NO_2, R' = Et, 82%, Z/E > 95/5
3f[b]: R = CF_3, R' = Me, 73%, Z/E > 95/5

3g[b]: 68%, Z/E > 95/5

3h: R = Me, 68%, Z/E > 95/5
3i: R = Et, 64%, Z/E > 95/5
3j: R = tBu, 73%, Z/E > 95/5

3k: 83%, Z/E > 95/5

3l: 83%, Z/E = 93/7

3m: 73%, Z/E > 95/5

3n[b]: 81%, Z/E = 90/10

3o: 80%, Z/E > 95/5

3p: 68%, Z/E= 93/7

3q: 35%, Z/E = 85/15

3r: 91%, Z/E = 62/38,

3s[b]: 63%, Z/E > 95/5

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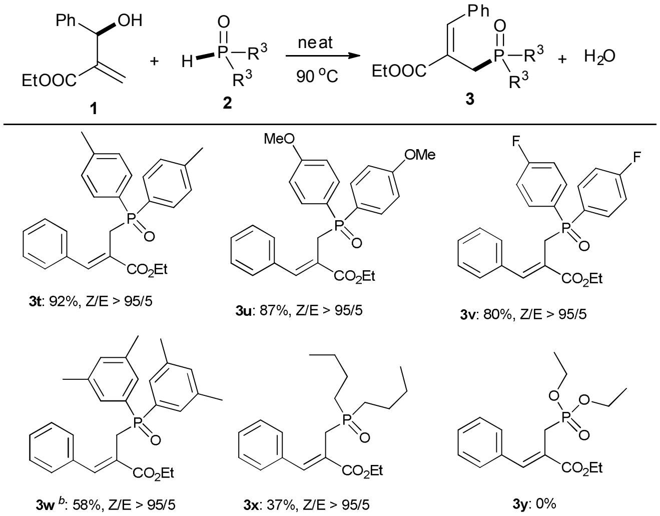
[a] Experimental conditions see General method. [b] Reactions performed at 60 °C.

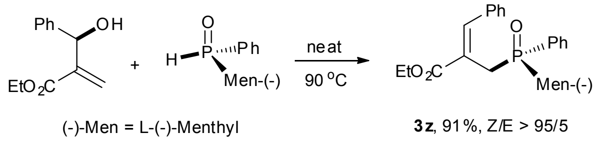
Subsequently, we examined the scope of the phosphine oxides using coupling partner **1a** and the results are listed in Table 3. Typical diarylphosphine oxides with electron-donating and electron-withdrawing substituents on aryl were well tolerated affording corresponding **3t**-**3v** in high yield with high selectivity. In addition, phosphine oxides with multi-substituents worked well and **3w** can be obtained in moderate yield which might be attributed to the steric hindrances effect. Dialkylphosphine oxide was also proved to be the suitable substrate for transformation (**3x**).

Table 3. Substrate scope for phosphine oxidants [a]



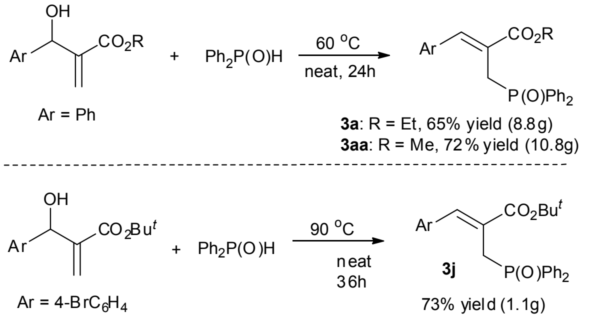
Reactions performed under the standard conditions. [b] DMSO (2.0 mL) as the solvent.

It should be noted that these secondary phosphine oxides are readily available from reactions between diethyl phosphonate and the corresponding organolithium or Grignard reagents. [17] Theoretically, a variety of phosphorus functionalities have the potential to be incorporated into allylic framework conveniently by using this method. For example, the P-stereogenic (R_P)-(-)-Menthylphosphine oxide[18] was successfully introduced into allylic skeleton with high yield and Z/E selectivity (Scheme 2). The configuration of phosphorus was stable and maintained (R_P/S_P > 99/1), no isomerization process was detected.



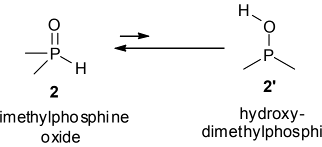
Scheme 2. Incorporating P-stereogenic phosphine oxide into allylic skeleton.

The C-OH/P-H dehydrative cross-coupling reaction also can be performed well even in 10 grams scales with comparable yield and selectivity. The allylic alcohol with *tert*-butyl ester was suitable substrate for gram scale reaction (Scheme 3).



Scheme 3. The grams scale reactions and synthetic application of allylic phosphorus.

With attempt to gain further insight into the mechanism involved, Density functional theory (DFT) calculations were conducted at a B3LYP/6-31+G(d) level. [19] We proposed the transformation might occur through two pathways: direct dehydrative coupling through a formal concerted process (Path A) or stepwise process *via* a Michael addition then followed by dehydration reaction of alcohol (Path B). We selected dimethylphosphine oxide **2** as model for the mechanism study. According to the substantial agreement among chemists, dimethylphosphine oxide undergoes dimethylphosphine oxide (**2**)–hydroxydimethylphosphine (**2'**) tautomerism. [3,20] The compounds almost existed entirely in the form of former isomer **2** under neutral conditions, while the later version **2'** is reactive and believed to be the actual nucleophilic species in the bond formation step. [20b]



(1)

As it's shown in Figure 1, the reaction is triggered by nucleophilic addition of hydroxydimethylphosphine **2'** to the active double bond of allylic alcohol. In path A, calculations indicated that "mutual aid effect" occurred between allylic alcohol and phosphine oxides. The hydrogen bond between the hydroxyl group of alcohol and hydroxydimethylphosphine favored the existence of **2'** and accelerated the following nucleophilic addition with a free energy of activation of 15.7 kcal mol^{-1} (**TS1**). At the same time, the C-O bond in alcohol was greatly activated by hydrogen bond with the generation of zwitterionic intermediate **IM1**, which was followed by a barrier-less process (**TS2**) to give the desired product with Z selectivity and H_2O. Thus, that was a formal concerted process and is favourable thermodynamically releasing 23.5 kcal/mol.
Theoretically, the dehydrative coupling might also proceeded stepwise (path B). Initially, the hydrogen bond between ester group and hydroxydimethylphosphine **2'** could promote the nucleophilic addition. The computed activation free energy of this addition process from starting materials to **IM1'** is 16.3 kcal/mol, which is slightly higher than **TS1**. **IM1** then isomerized to **IM2'**. Finally, the rate-determining step from **IM2'** to **E-3** occurred with 19.5 kcal/mol computed activation

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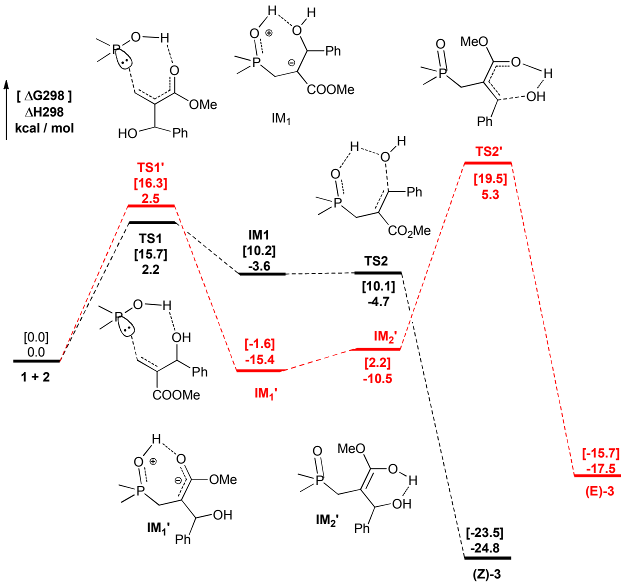
free energy. Compared with path B, path A is favoured in activation free energy. Moreover, Z-selectivity for path A is in accordance with the result of X-ray analysis (**3j**).

Figure 1. DFT computed energy surface for the dehydrative cross-coupling. B3LYP/6-31+G(d) level. Path A: (**TS1-IM1-TS2**); Path B: (**TS1'-IM1'-IM2'-TS2'**).



Conclusions

In conclusion, we developed the first C-OH/P-H dehydrative cross-coupling reaction between MBH alcohol and phosphine oxides. This is an atom-economical and environmentally benign approach for P-C bond construction with water as the only by-product. This reaction proceeded smoothly without any catalyst and additive in solvent-free manner to deliver the desired product with wide tolerance. A variety of allylic phosphorus compounds can be obtained in good to excellent yields with high Z-selectivity. DFT calculation indicated that the direct dehydrative coupling through a formal concerted process. In the key transition state, the intermolecular hydrogen bond stabilize hydroxydiaryl(alkyl)phosphine, accelerate nucleophilic addition, and active C-O bond.

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