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Allylic Phosphorus Ylides Directly Generated from Alcohols with Water as the Only Byproduct

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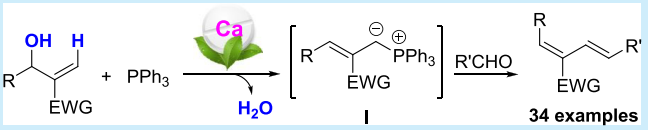
Supporting Information

ABSTRACT: A novel strategy for the preparation of allylic phosphorus ylides directly from Morita−Baylis−Hillman (MBH) alcohols in an environmentally benign manner was developed. With the assistance of a calcium catalyst, the S_N2' process between phosphines and allylic alcohols occurred smoothly, delivering allylic phosphorus salts and calcium-stabilized hydroxide ions. Then, in situ deprotonation gave the allylic phosphorus ylides with water as the only byproduct. Functionalized 1,3-diene moieties can be conveniently obtained by trapping the ylides through a Wittig olefination.



Phosphorus ylides have attracted increasing attention and emerged as versatile building blocks in various transformations[1] beyond traditional olefinations.[2] In classic methods, ylides are prepared from the corresponding organic halides using a stoichiometric base, producing stoichiometric amounts of the halide salt, which is far from ideal based on synthetic efficiency and environmental concerns (Figure 1a).[3] In some special cases, allenoates,[4] activated alkenes,[5] and alkynes[6] have been identified as suitable precursors to produce the corresponding phosphorus ylides;[7] however, these substrates were generally derived from organic halides and/or required tedious preparation and purification processes.[7] We envision that ideally, in terms of step and atom economy and environmental impact, the synthetically suitable alcohols could be directly converted into phosphorus ylides, delivering water as the only byproduct (Figure 1b). In our design, the key factor was to identify a catalyst that can efficiently activate the C−OH bond and allow the subsequent S_N2 process involving the phosphine to occur smoothly. Following the S_N2 process, the in situ generated hydroxide ion (stabilized by the catalyst) then deprotonates the phosphonium intermediate, delivering the corresponding ylide with water as the only byproduct.

Since 2003, allylic phosphorus ylides **I** (Figure 1c) have been demonstrated to be one of the most powerful and versatile synthetic intermediates in diverse annulations[7b,d,g,h] in addition to Wittig olefinations[8] and Krische allylations.[9] Pioneering 1,3-dipolar [3 + *n*] (*n* = 2, 3, 4, and 6) cycloadditions[10] with active alkenes were independently developed by Lu[10a] and Tang.[10b] Asymmetric versions have been developed by Tang,[10e] Barbas,[10i,o] Lu,[10h,j] Shi,[10g,k−m] Liu,[10n] Zhong,[10p] Guo,[10p,r,s] and Chen.[10t] A powerful [1 + 4] annulation[11] was then

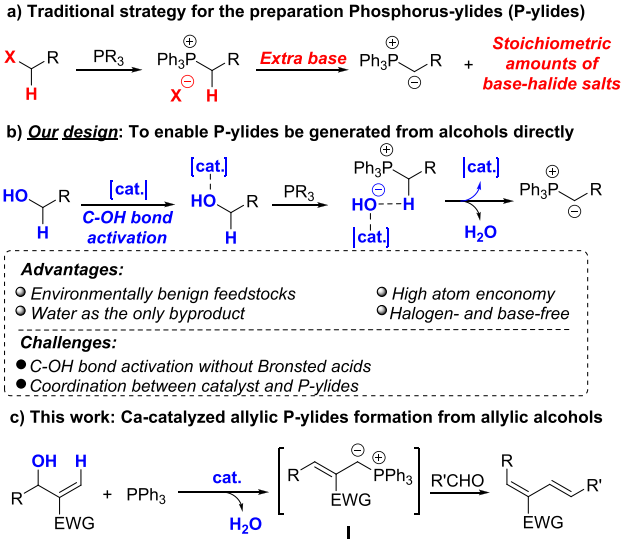


Figure 1. Strategies for preparing phosphorus ylides. (a) Traditional methods with organic halides; (b) our environmentally benign method; (c) this investigation: to obtain synthetically powerful allylic phosphorus ylides.

reported by the Zhang,[11a] Huang,[11b] and He[11c] groups. Huang's group has explored the synthetic utilities of allylic ylides in detail and realized various amazing [2 + 4],[12] [3 + 3],[13] [3 + 4],[14] etc.[15] annulations for accessing diverse,

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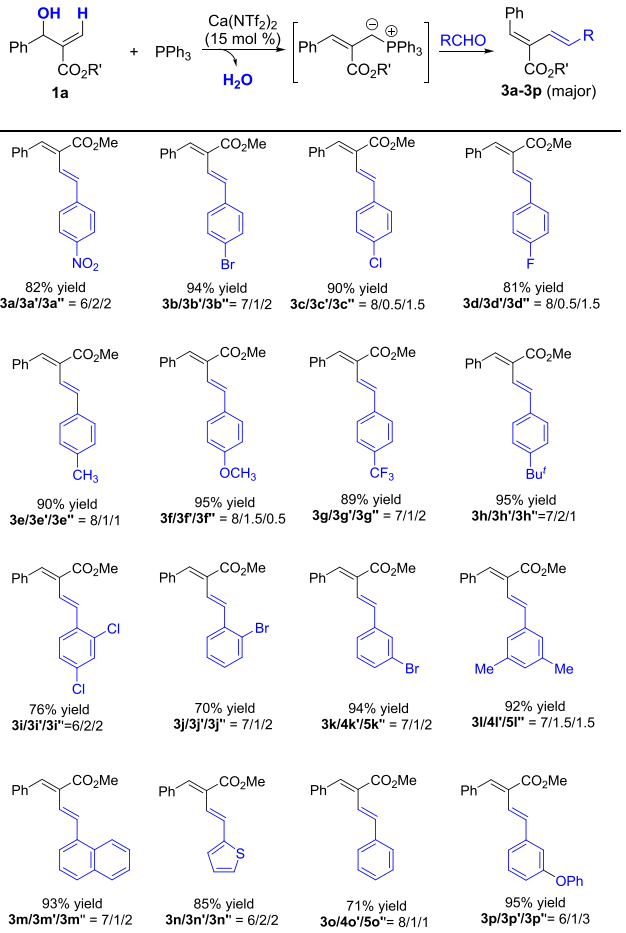
synthetically challenging frameworks with high efficiency. Recently, asymmetric versions of [1 + 4] annulations have also received great attention, and substantial contributions have been made by the groups of Shi,[16a−c] Li,[16d] and He.[16e] Asymmetric [3 + 3] annulations were also documented by Guo[17] and co-workers. Among these investigations, it is widely recognized that only MBH adducts (including halides, acetates, and *tert*-butyl carbonates) are suitable precursors for ylides **I**, although these MBH adducts were derived from MBH alcohols with tedious conversion and purification processes in addition to the generation of stoichiometric byproduct.[7b,d] This can be ascribed to the remarkably high activation barrier of C−OH bond scission, which makes delivering phosphorus ylides **I** directly from MBH alcohols quite challenging.[8b] Furthermore, obstacles, such as the tendencies of MBH alcohols to decompose and polymerize, limit their direct synthetic utility. In our continuing effort to develop catalysts consistent with green and sustainable chemistry,[18] we selected MBH alcohols as substrates (Figure 1c) to explore the feasibility of our design, and to attempt to obtain allylic phosphorus ylides **I**. Herein, we successfully developed a calcium catalyst that enabled the desired protocol to occur smoothly in isopropanol as the solvent with water as the only byproduct. In this reaction, allylic phosphorus ylide **I** (Figure 1c) intermediates were trapped by a Wittig olefination, producing synthetically useful 1,3-diene moieties in high to excellent yields.

We first explored the reaction between methyl 2-(hydroxy(phenyl)methyl)acrylate (**1a**) and triphenylphosphene (**2a**) in toluene as the solvent. 4-Nitrobenzaldehyde was selected to trap the desired allylic phosphorus ylides through a Wittig olefination process. Given our interest in indium catalysis, the strong Lewis acid $In(OTf)_3$ was first introduced into the reaction. After 50 h, the desired product, methyl (*E*)-2-((*E*)-benzylidene)-4-(4-nitrophenyl)but-3-enoate[19] (**3a**, CCDC: 1889054) was detected in 26% yield (Supporting Information (SI), Table S1, entry 1). Much lower yields or no product resulted when other traditional Lewis acids, such as $InCl_3$, $Sc(OTf)_3$, $Fe(OTf)_2$, $FeCl_3$, and $AlCl_3$, were used under the same conditions (SI, Table S1, entries 2−6). Then, we switched our attention to alkaline earth metals, which are abundant and well established as a powerful catalyst in Friedel−Crafts and related cationic cycloadditions[20−22] by Niggemann,[20] Gandon,[21] and other groups.[22] To our delight, $Ca(NTf_2)_2$ delivered a substantially better yield (45%) of **3a** (SI, Table S1, entry 7). $Ca(OTf)_2$ and $Ba(NTf_2)_2$ give slightly lower yields (SI, Table S1, entries 8−9). To improve the yield of **3a**, the effects of solvent and additives were then investigated (SI, Table S2, entries 1−7). Screening solvents revealed that isopropanol facilitated the transformation and enabled the transformation in 3 h (SI, Table S2, entry 7). However, the reaction mixture was complex, and **3a** was detected in comparable yields (38%). In further investigations, we found that both a trace amount of water and a high reaction concentration favored the transformation (SI, Table S3, entries 1−3), probably by accelerating the deprotonation in the phosphorus ylide formation step. Negative effects were observed upon increasing or decreasing the reaction temperature (SI, Table S3, entries 4−7). The addition of CF_3COOK as an additive can alter the reaction by suppressing side reactions (SI, Table S3, entries 8−9), increasing the yield of **3a** (up to 82% isolated yield); however, a longer reaction time was required. No increase in yield or selectivity can be achieved by altering the nucleophilicity or hardness of the phosphine (SI, Table S3, entries 10−13).

Under the optimized conditions, the substrate scope was then investigated. As shown in Scheme 1, the in situ generated

Scheme 1. Substrate Scope of Aldehydes[a]



[a]Experimental conditions: **1a** (0.6 mmol) and aldehyde (0.4 mmol), $Ca(NTf_2)_2$ (15 mol %), PPh_3 (1.2 equiv), CF_3COOK (30 mol %), and water (1.3 equiv) in isopropanol (1.0 mL) under a N_2 atmosphere for 24 h. Isolated total yield (major products (2*E*,3*E*)-diene (**3**) and minor isomer (2*Z*,3*E*)-diene (**3′**) and (2*E*,3*Z*)-diene (**3′′**)). The ratio of **3**/**3′**/**3′′** was determined by crude ^1H NMR.

allylic ylide can be trapped by various aromatic aldehydes, delivering 1,3-dienes in good to excellent yields with moderate to high stereoselectivities. Both electron-withdrawing (**3a**−**3g**) and electron-donating (**3e**−**3f**, **3i**, and **3p**) groups on the phenyl ring were amenable to this protocol. The positions of the substituents (at the *para* or *meta* positions) of the phenyl ring have limited effects on the overall transformation (**3b**, **3j**, and **3k**). Even 4-(*tert*-butyl)benzaldehyde was well tolerated and delivered the corresponding product in excellent yield (**3h**). However, the *ortho*-substituted phenyl aldehydes, such as 2,4-dichlorobenzaldehyde and 2-bromobenzaldehyde, afforded the desired products (**3i** and **3j**) in slightly lower yields. This can be attributed to the steric hindrance disfavoring the Wittig olefination. Monosubstituted and polysubstituted, as well as fused-aromatic, aldehydes smoothly reacted with phosphorus ylides under the identified conditions (**3i**, **3l**, and **3m**). Moreover, thiophene-2-carbaldehyde was a suitable substrate

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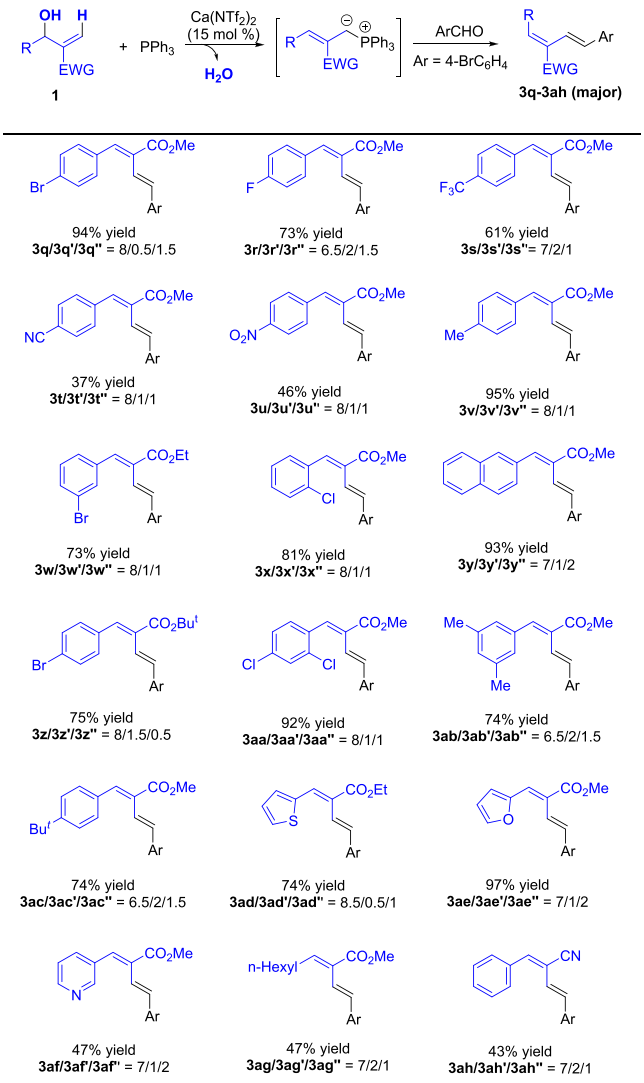
for this reaction (**3n**). In the presence of aliphatic aldehydes (butyraldehyde), the decomposition of methyl 2-(hydroxy(phenyl)methyl)acrylate overwhelmed the formation of the allylic phosphorus species and thus disfavored the desired 1,3-diene generation.

Subsequently, we explored the scope of this transformation with respect to MBH alcohols. The result is shown in Scheme 2. A variety of MBH alcohols were effectively reacted with 4-bromobenzaldehyde to afford the desired products in moderate to excellent yields with good selectivities. The electronic properties and the position of the substituents on the phenyl ring of the MBH alcohols have limited effects on the overall performance in terms of the yield and selectivity (**3q**−**3x**). It should be noted that allylic alcohols bearing highly active groups such as cyan (**3t**), nitryl (**3u**), and trifluoromethyl (**3s**) could furnish the desired products in good yields. Sterically demanding MBH alcohols bearing naphthalene-1-yl (**3y**), 2,4-dichlorophenyl (**3aa**), and 3,5-dimethyl (**3ab**) moieties were compatible with this process. A *tert*-butyl group, either on the phenyl ring (**3ac**) or as an ester (**3z**), has little effect on the yield or selectivity. As expected, heteroaryl substituted MBH alcohols, such as thiophen-2-yl (**3ad**), furan-2-yl (**3ae**), and pyridien-2-yl (**3af**), were also well tolerated. Remarkably, an MBH alcohol with an alkyl substituent can also be successfully incorporated into the desired 1,3-diene skeleton (**3ag**). Moreover, 2-(hydroxy(phenyl)methyl)acrylonitrile can deliver the corresponding 1,3-diene in moderate yield (**3ah**). This result indicated that the ester group on the MBH alcohols was not required. Unfortunately, allylic alcohols other than MBH derivatives were inefficient under the developed conditions.

Scheme 2. Substrate Scope of the MBH Alcohols[a]



[a]Experimental conditions: **1** (0.6 mmol) and aldehyde (0.4 mmol), $Ca(NTf_2)_2$ (15 mol %), PPh_3(1.2 equiv), CF_3COOK (30 mol %), and water (1.3 equiv) in isopropanol (1.0 mL) under a N_2 atmosphere for 24 h. Isolated total yield (major products (2*E*,3*E*)-diene (**3**) and minor isomer (2*Z*,3*E*)-diene (**3′**), (2*E*,3*Z*)-diene (**3″**)). The ratio of **3**/**3′**/**3″** was determined by crude ^1H NMR.

To gain more insight into the catalysis, ^{31}P NMR monitoring experiments were conducted in an NMR tube (Figure 2). As shown in Figure 2, without the catalyst, there is no interaction between PPh_3 and **1a** (stacking ^{31}P NMR spectrum 2). In addition, a coordination effect was detected for $Ca(NTf_2)_2$ with PPh_3 (stacking ^{31}P NMR spectrum 3). These results, to some extent, revealed that PPh_3 is free under these Lewis basic reaction conditions. With the assistance of both PPh_3 and $Ca(NTf_2)_2$, **1a** can then be consumed to generate the corresponding ylide (stacking ^{31}P NMR spectra, 5). By introducing an aldehyde, the Wittig olefination proceeded smoothly and served as the driving force for the conversion of the allylic alcohols to the corresponding ylides (stacking ^{31}P NMR spectra 6−8).

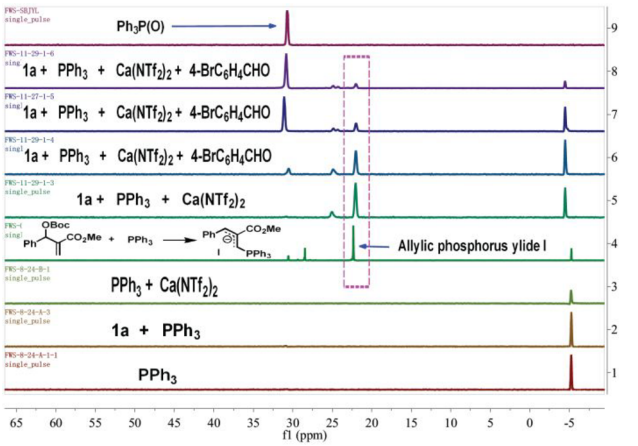


Figure 2. Stacking ^{31}P NMR spectra. Experiments were conducted in *i*-PrOH-d8.

The reaction mechanism shown in Figure 3 was then proposed. Judging from the positive influence of water and trifluoroacetate anions as well as the related investigation concerning calcium coordination, the eight coordination sites of calcium catalyst **A**[23] may be occupied by water, NTf^-, and trifluoroacetate anions. Initially, the C−OH bond was activated by calcium catalyst **A** through coordination to the hydroxyl oxygen (**B**). Subsequently, the allylic S_N2 process between the phosphine and intermediate **B** gave ion pair **C**, in which the hydroxyl ion was stabilized by calcium. Then, proton transfer in the ion pair delivered the desired allylic ylide **I** and regenerated the catalyst. The proton transfer process was accelerated by the protic solvent (*i*-PrOH), which was identical to what was observed in our previous study.[24]

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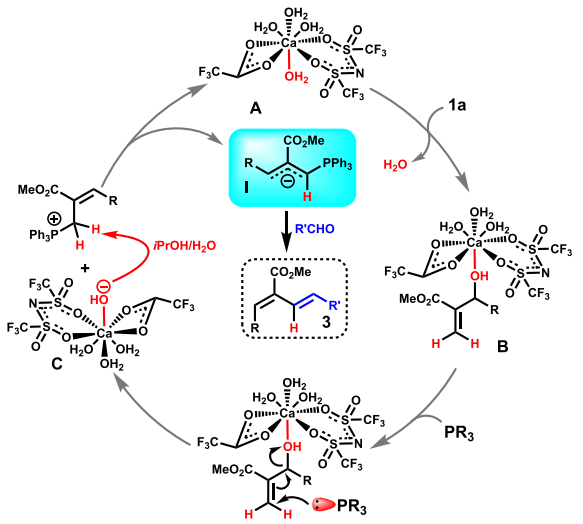

Figure 3. Proposed mechanism.

The 1,3-diene moiety has been proven to be a versatile synthetic intermediate for further elaboration. For instance, the Diels–Alder reaction of **3o** with DMAD in toluene afforded dehydrobenzene derivative **4**, a key intermediate for preparing polysubstituted benzenes[25a] (Figure 4). In addition, an

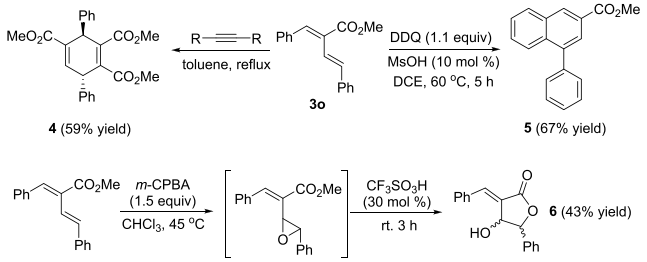

Figure 4. Elaboration of the 1,3-diene skeleton.

intramolecular arene–alkene oxidative coupling[25b] can also proceed smoothly to give **5** in the presence of DDQ and a catalytic amount of MsOH. Moreover, **3o** can also serve as a precursor for preparing 3-benzylidenelactone skeletons[25c] **6**.

In conclusion, a novel strategy for the preparation of allylic phosphorus ylides from MBH alcohols with a wide functional group tolerance was developed. In this protocol, a calcium catalytic system can efficiently activate the C–OH bond and then enable the subsequent S_N2 process involving the phosphine, to smoothly deliver the allylic phosphorus salts and calcium stabilized hydroxide ions. Then, an in situ deprotonation gave the allylic phosphorus ylides with water as the only byproduct. A variety of functionalized 1,3-diene moieties can be conveniently obtained by trapping the ylides through olefination reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01349.

Experimental procedures, and screening reaction conditions, analytical data for all new compounds, NMR spectra of products (PDF)

Accession Codes

CCDC 1889054 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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