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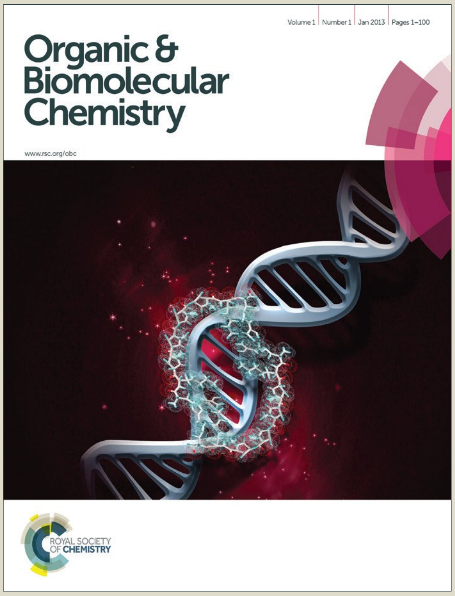

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ARTICLE TYPE

Copper-Catalyzed Allylic C-H Phosphonation

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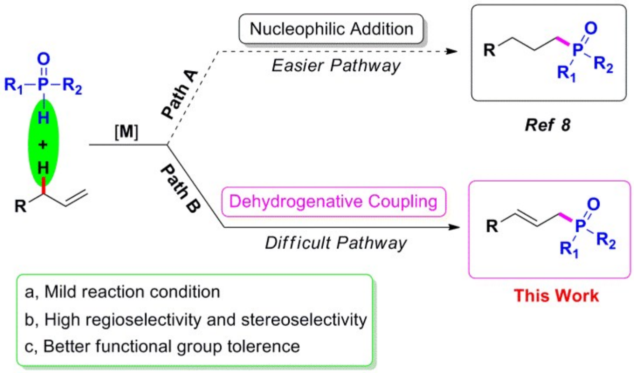
An efficient copper-catalyzed allylic C-H phosphonation reaction has been developed under mild reaction conditions. This method exhibits high regioselectivity and stereoselectivity. Various alkenes with useful functional groups are compatible in this transformation. Preliminary mechanistic studies reveal that the *p*H value and the loading of Ag-salt were the key factors to change the composition of products.

Introduction

Allylphosphonates are synthetic intermediates valuable for application in pharmaceutical chemicals, agrochemicals, organic synthesis, material science, as well as in biochemistry.[1] As a consequence, the development of more concise and efficient methodologies for synthesis allylphosphonates is desirable but presents a challenge. At present, advancements mainly include hydrophosphination of allenes[2] and transition-metal-catalyzed Heck reactions[3] and cross-coupling reactions with allyl-halides or carboxylic esters.[4] However, all the aforementioned methods generally require a specifically functionalized precursor which limits their application in scope. Recently, transition metal-catalyzed allyl C-H bond functionalizations have garnered much attention because of their wide scope and high atom economy,[5, 6, 7] which also provide a novel and potentially rewarding strategy for the synthesis of allylphosphonates by direct phosphonation of allyl C(sp^3)-H bonds. To date, however, the direct allylic phosphonation reaction has yet to be established. It is well known that P(O)-H compounds are the best nucleophiles which are easily added to the double bonds of alkenes and lead to hydrophosphination frequently (Path A, Scheme 1);[8] indeed, the allylic phosphonation reaction is very difficult to control. Furthermore, achieving high regioselectivity and stereoselectivity represents a giant challenge for the allylic phosphonation reaction. In the past few years, we have been committed to unveiling novel organophosphorus transformations,[9,10b] and recently we disclosed a copper-catalyzed direct dehydrogenative allylic phosphination to synthesize allylphosphonates (Path B, Scheme 1). Gratifyingly, the hydrophosphination product is almost completely suppressed in our reaction. It is worth noting that high regioselectivity and stereoselectivity are also achieved in our reaction system. In addition, our new reaction starts with simple allyl-compounds without pre-functionalizing and shows good functional group tolerance.

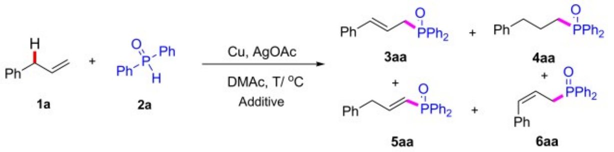


Scheme 1 Copper-catalyzed Allylic C-H Phosphonation Reaction

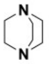
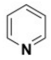
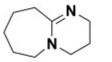
Results and discussion

Initially, our study began with allylbenzene (**1a**) and diphenylphosphine oxide (**2a**) in the presence of 10 mol % Cu_2O and 2.0 equiv of AgOAc in DMAc at 90°C under an argon atmosphere (Table 1, entry 1). We were very excited to find that an allyl phosphorylated product (**3aa**) can be detected as the major product with a mixture of other three byproducts and to our surprise no branched products were detected. Encouraged by this result, next we needed to improve the yield and the ratio of **3aa** in all products. Initially, the total yield improved when we reversed the ratio of **1a** and **2a**, but as a result of this shift, **4aa** became the major product (entry 2), which indicated more phosphorus leads hydrophosphination. Next, we employed other oxidants and found that AgOAc was still the best choice (see the Supporting Information). We were surprised to find that the addition of 2.0 equiv DABCO (1, 4-diazabicyclooctane) as a base, the yield and the ratio improved significantly (entry 3). Other bases produced poorer performance (entries 4-5). Reduced the loading of DABCO to 30 mol %, the three byproducts were almost entirely suppressed (entry 6). But if the loading of DABCO was reduced more, we observed no improvements (entry 7). This indicates that base-loading represents a crucial factor affecting selectivity. Furthermore, lowering the reaction temperature to 70 °C, increased the yield to 64 % (entry 8). The reaction could not occur at a lower temperature (entry 9). When we changed the ratio of **1a** / **2a** to 3: 1, the yield reached 74 % (entry 10). Notably, using 3.0 equivalent AgOAc resulted in 81 % yield with a trace amount of byproducts (entry 11). Use of more AgOAc decreased the yield (entry 12). Other copper salts were screened, but none performed better than Cu_2O (entries 13-15). It is important to note that in the absence of AgOAc or Cu_2O in the reaction system, we only got **4aa** (entries 16-17). Without addition of DABCO, the yield of product decreased to 21% with relative lower ratio (entry 18). Supporting Information lists optimization information in more detail.

Table 1 Reaction Conditions Screening.[a]



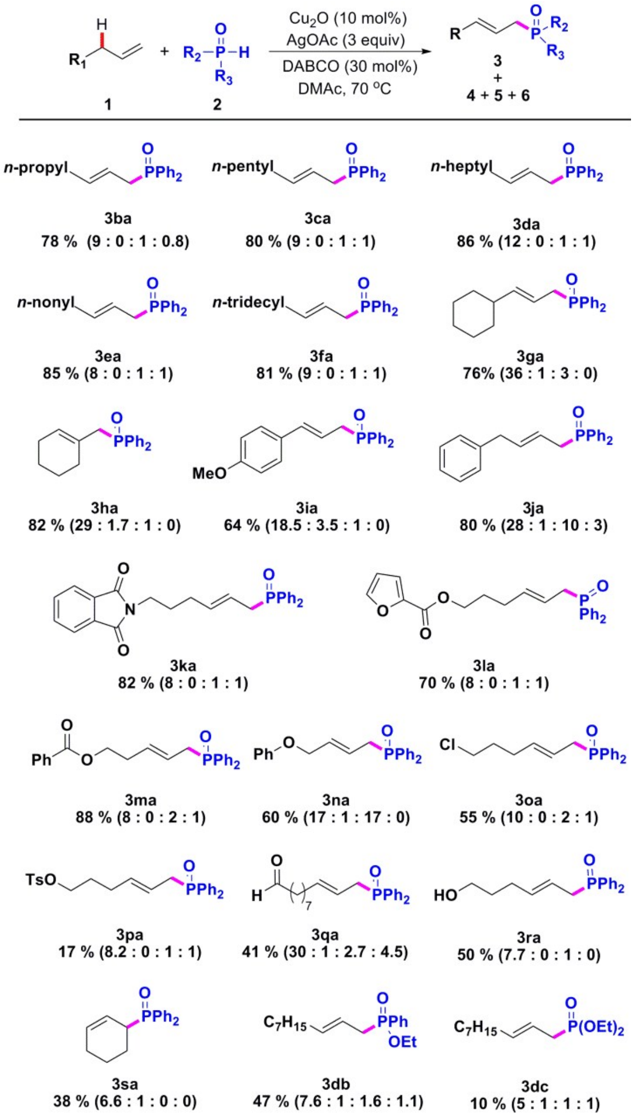
Entry	Cu (10 mol %)	1a / 2a	AgOAc (equiv)	Base (equiv)	T / °C	Yield (%) [b]	3aa:4aa:5aa:6aa [c]
1	Cu_2O	2 : 1	2.0	-	90	33	12 : 2 : 2 : 1
2	Cu_2O	1 : 2	2.0	-	90	68	7 : 28 : 1 : 3
3	Cu_2O	2 : 1	2.0	**B1** (2.0)	90	56	43 : 10 : 1 : 2
4	Cu_2O	2 : 1	2.0	**B2** (2.0)	90	33	44 : 2 : 12 : 3
5	Cu_2O	2 : 1	2.0	**B3** (2.0)	90	trace	-
6	Cu_2O	2 : 1	2.0	**B1** (0.3)	90	56	16 : 1 : 1 : 1
7	Cu_2O	2 : 1	2.0	**B1** (0.2)	90	54	14 : 1 : 1.5 : 1
8	Cu_2O	2 : 1	2.0	**B1** (0.3)	70	64	14 : 1 : 2 : 1
9	Cu_2O	2 : 1	2.0	**B1** (0.3)	50	trace	-
10	Cu_2O	3 : 1	2.0	**B1** (0.3)	70	74	15 : 1 : 1 : 1.5
11	**Cu_2O**	**3 : 1**	**3.0**	**B1 (0.3)**	**70**	**81**	**20 : 1 : 1 : 1.5**
12	Cu_2O	3 : 1	4.0	**B1** (0.3)	70	70	20 : 1 : 1 : 2
13	CuTc	3 : 1	3.0	**B1** (0.3)	70	64	10 : 1.6 : 1 : 1
14	CuOTf	3 : 1	3.0	**B1** (0.3)	70	71	9 : 2 : 1 : 1
15	$CuBr_2$	3 : 1	3.0	**B1** (0.3)	70	42	13 : 2 : 1 : 2
16	-	3 : 1	3.0	**B1** (0.3)	70	38	**4aa**
17	Cu_2O	3 : 1	-	**B1** (0.3)	70	60	**4aa**
18	Cu_2O	3 : 1	3.0	-	70	21	17 : 2 : 2.6 : 1

B1  **B2**  **B3** 

[a] The reactions were conducted on a 0.2 mmol scale under the following reaction conditions: **1a**, **2a**, Cu (10 mol %), AgOAc, DMAc (2.0 mL) and additive under Ar for 10h, DMAc= *N*, *N*-dimethylacetamide; [b] Total yield of isolated products; [c] Determined by ^1H NMR and ^{31}P NMR.

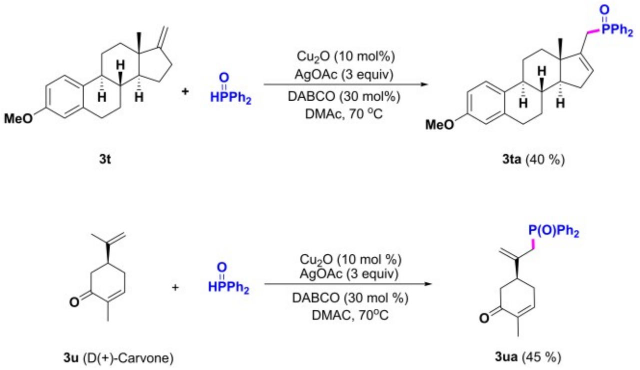
Upon optimization of the reaction conditions, we examined the scope of this reaction and found that a series of olefins were applicable to the transformation (Table 2). In most of the reactions, we observed that compound **3** was generated as the major product, whereas compounds **4**, **5** and **6** were produced as byproducts. The reaction of simple alkenes with different carbon chain lengths proceeded efficiently (**3ba-3fa**). For the cycloalkane-substituted alkenes, we observed good yields and few byproducts regardless of whether the double bonds were located in the ring or outside the ring (**3ga** and **3ha**). The 4-Allylanisole and 4-Phenyl-1-butene underwent the reaction smoothly and produced moderate- to good yields (**3ia** and **3ja**). A range of functional groups, including amide (**3ka**), heteroaromatic rings (**3la**), and ester (**3ma**) was also tolerated well in this reaction. When we changed the substituent to phenyl ether (**3na**), the major products became **3** and **5** with a ratio of 1: 1. It is worth noting that the halogen-substituted olefin was also applicable (**3oa**) and it provided the condition for a further transformation. The *p*-toluenesulfonyl (Ts) ether protecting group was also tolerated, but with a lower yield (**3pa**). Remarkably, the aldehyde group (**3qa**), which is incompatible under oxidative conditions, still remained intact in this reaction. The free hydroxyl (**3ra**) was also unaffected and the desired product was obtained in a moderate yield. To our delight, the internal alkene cyclohexene could also react with **2a,** thus affording the corresponding phosphorylate cycloalkene structure (**3sa**). In addition to diphenylphosphine oxide (**2a**), ethyl phenylphosphinate (**2b)** and diethyl phosphite (**2c)** were also candidates for this transformation, underwent phosphorylation to obtain products **3db**, **3dc** but with lower yields.

Table 2 Scope of Allylic Phosphorylation [a, b ,c]



[a] alkene 1 (0.6 mmol), 2 (0.2 mmol), Cu_2O (10 mol %), AgOAc (0.6 mmol), DABCO (30 mol %) in 2 mL DMAc at 70 °C for 10h; [b] The given yield represents the total yield of four products; [c] The ratio of 3:4:5: 6 was determined by ^{31}P NMR and is shown in the parentheses.

The simplicity and convenience of the metal-catalyzed direct C-H functionalization approach lends itself well to wide applications within the fields of natural products modification. Phosphonation is a common method used in medicinal and ligand-synthesis; indeed, direct allylic phosphonation may prove quite useful. To demonstrate the potential, we subjected the derivative of estrone (**3t**) to copper-catalyzed allylic C-H phosphonation conditions (Scheme 2). The allylic phosphonation product **3ta** was isolated in 40 % yield. The natural product D(+)-Carvone (**3u**) also underwent the reaction smoothly and produced **3ua** with high regioselectivity which may be potential chiral P/olefin ligand.

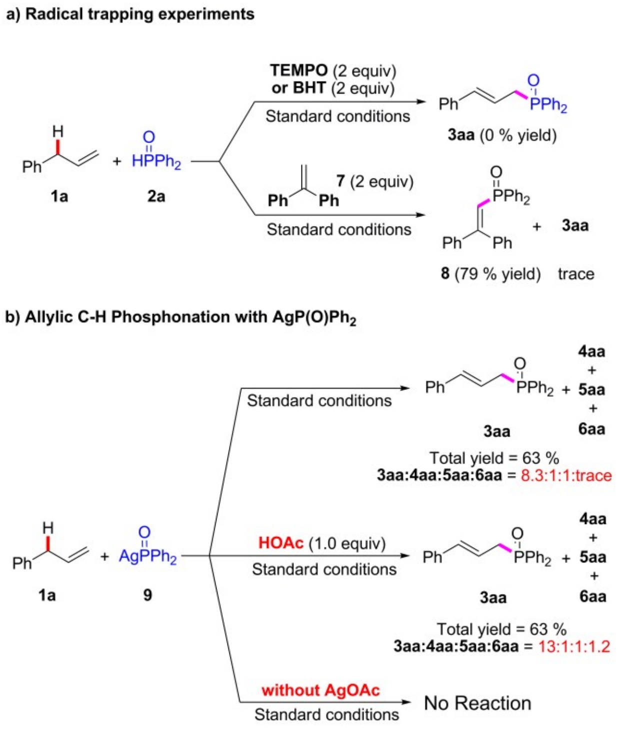


Scheme 2 Direct Phosphonation of Derivatives of Natural Product

In order to gain insight into the mechanism of this transformation, preliminary mechanistic studies were carried out. First, we surveyed a series of control experiments. In the radical trapping experiments (a, Scheme 3), the reaction was completely suppressed in the presence of 2.0 equiv. TEMPO or BHT. Furthermore, the addition of 1, 1-diphenylethylene (**7**) led to a compete reaction, yielding the alkenyl diphenylphosphine oxide **8**. The above results indicate that a [P(O)Ph_2] radical was involved in this reaction. We deduced that the first step involves phosphonation with AgOAc.[10] Thus, some experiments of allylic phosphonation with AgP(O)Ph_2 were carried out (b, Scheme 3). When [Ph_2P(O)Ag] **9** replaced **2a**, **3aa** could be obtained smoothly under standard conditions. It is important to note that adding 1.0 equiv HOAc to such reaction, the selectivity was significantly improved. This result implies that the *p*H of the reaction system may be a key factor to change the composition of products. In addition, when employing **9** as substrate in the absence of AgOAc, no products were detected. This indicates that AgOAc plays roles beyond the formation of complex **9**.

Second, in order to arrive at a clear understanding of this reaction, we tested the *p*H value of the reaction system at different time points. As shown in the chart (Figure 1, C-A), the *p*H value of the proceeding reaction system gradually declined in the first three hours until it reached its lowest value. The *p*H value rose from this point as the reaction continued and then maintained a stable value. This result proves that over the course of the reaction HOAc was first generated and then neutralized.

Third, in the process of optimizing the reaction, we found that major product differed depending on what equivalents of AgOAc we used (Figure 1, C-B). When we ignored other byproducts, we found that the major product changed from **4aa** to **3aa** gradually along with the increase of AgOAc-equivalents. When the above experimental results were combined (Scheme 3, b), we speculated that in addition to the formation of complex **9**, AgOAc might be used as an oxidant to promote the cycle of Cu^I to Cu^{II}.



Scheme 3 Control experiments

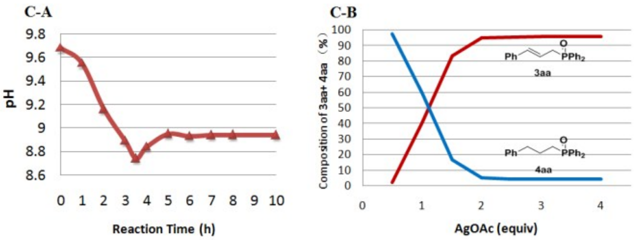
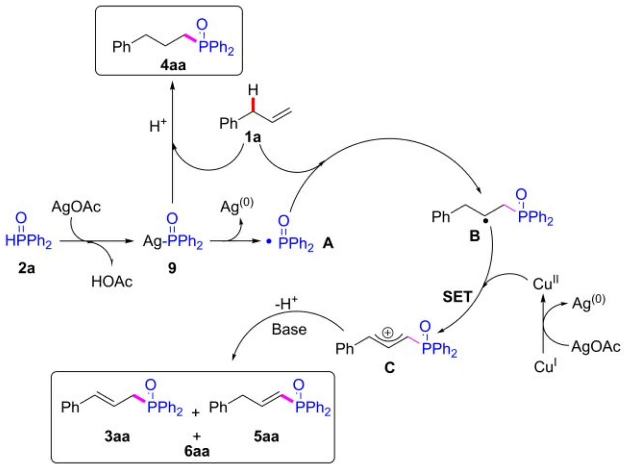


Figure 1 (C-A): *p*H values at different time points. (C-B): Composition of **3aa** + **4aa** under different equivalents of AgOAc.

Based on the above analysis, we proposed a plausible pathway involving a free phosphorus radical species (Scheme 4). Initially, diphenylphosphine oxide **2a** reacts with AgOAc to form the complex 9.[10] In the presence of a small amount of AgOAc, hydrophosphination becomes the main reaction to form **4aa**. Our previous experiments have further proved this result (Figure 1, C-B). The reactive species A is then generated from 9.[10, 11] Next, the addition of P-radical A to **1a** gives the allyl radical intermediate B. Subsequently, an allyl-cation type C is formed via a single-electron transfer (SET) process. Finally, coordinated by base, selective deprotonation of C results in the desired product **3aa** and the isomers **5aa**, 6aa. In this pathway, the pH value which was regulated by the base and the loading of AgOAc may be the decisive factor in the composition of products. However, the exact role of the base is still unclear.



Scheme 4 Plausible Mechanistic Pathway

Conclusions

In summary, we have developed an efficient and selective copper-catalyzed oxidative phosphonation reaction. In this transformation, the formation of C (sp^3)-P bond is achieved. Under mild conditions, a variety of allylic phosphinylated products were obtained in high regioselectivity and stereoselectivity. Further investigations to clarify the reaction mechanism are currently underway in our laboratory.

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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