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Stereoselective synthesis of vinylphosphonates and phosphine oxides *via* silver-catalyzed phosphorylation of styrenes†

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An efficient and stereoselective synthesis of vinylphosphonates and phosphine oxides was developed starting from styrenes using $AgNO_3$ as the catalyst and $K_2S_2O_8$ as the oxidant. The success of the reaction was found to be critically dependent on the use of TEMPO as the additive.

Vinylphosphonates are a group of important compounds in synthetic chemistry and are commonly used to prepare biologically active molecules,[1] flame retardants,[2] and polymer additives.[3] In addition, vinylphosphonates are frequently used in organic transformations such as Michael additions[4a] and Horner–Wadsworth–Emmons reactions.[4b] For these reasons, the development of simple and stereoselective methods to prepare vinylphosphonates has become important in organic synthesis. Even though there are numerous methods for their syntheses,[5] those relying on the formation of vinylic carbon–phosphorous bonds by transition metal catalyzed cross coupling or addition reactions are particularly noteworthy due to their overall efficiency and selectivity.[6] Though transition metal catalyzed coupling of alkenyl halides or pseudo halides with *H*-phosphonate does provide useful ways of synthesizing vinylphosphonates (eqn (1)), the addition of *H*-phosphonates to alkynes is a 100% atom economical reaction since no waste is generated in the process and all the atoms in the starting materials are incorporated in the final products (eqn (2)). Consequently considerable efforts have been made by scientists on this research front and significant progresses have been made.[7–10] For example, Han and Tanaka in 1996 have reported an efficient Pd-catalyzed hydrophosphorylation of terminal alkynes, leading to the selective formation of a Markovnikov addition product.[7] By changing the catalyst from Pd to Rd and using a cyclic *H*-phosphonate, they were able to reverse the regioselectivity completely and (*E*)-alkenylphosphonates were obtained instead.[8]

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Later on, Han was able to effect the same transformation with a cheaper Ni-catalyst.[9] Complementary to these metal catalyzed processes, some radical initiated processes were also developed.[10] Although these approaches provided useful access to substituted vinylphosphonates, most of them suffered from some drawbacks such as lack of stereoselectivity (a mixture of *E*/*Z* products) or the need to use a rather expensive catalyst. As a result, there remains much room to be improved for the stereoselective synthesis of vinylphosphonates.
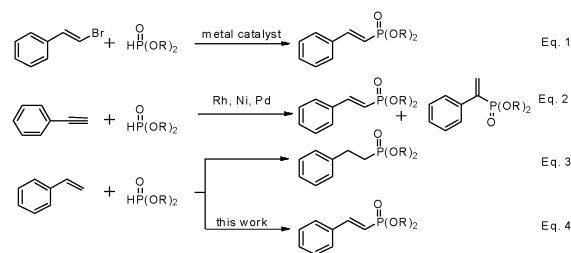
Olefins are basic building blocks in organic chemistry and using them as starting materials would be highly advantageous. However, the reaction of olefins with phosphite catalyzed by a transition metal catalyst or radically initiated, as reported by many chemists, usually gave the addition product (eqn (3)).[10e,11] Recently, Maiti reported a series of efficient nitration of olefins with silver nitrite,[12a] $Fe(NO_3)_3$[12b] or *tert*-butylnitrite[12c] *via* a nitro radical addition process. With the aid of TEMPO, they were able to obtain nitroalkenes instead of the saturated alkanes. Inspired by Maiti's results and the knowledge that phosphite could be utilized as a phosphoryl radical precursor, we wonder that vinylphosphonates can be synthesized directly from styrenes.[13] Herein we report vinylphosphonates can indeed be efficiently and stereoselectively synthesized from styrenes in good yields (eqn (4)).

Our investigation began with the reaction of styrene with diethyl *H*-phosphonate in the presence of 5 mol% of Ag_2CO_3, $K_2S_2O_8$ (2 equiv.) and TEMPO (0.4 equiv.) in toluene at 100 °C for 6 hours. Much to our delight, the desired product **2a** was indeed obtained even though the yield is very low (Table 1, entry 1). This result encouraged us to optimize the reaction

Table 1 Screening of reaction conditions[a]

Entry	Catalyst	Oxidant	Additive	Solvent	Yield[b] (%)
1	Ag_2CO_3	$K_2S_2O_8$	TEMPO	Toluene	<5
2	AgOAc	$K_2S_2O_8$	TEMPO	Toluene	12
3	$AgNO_3$	$K_2S_2O_8$	TEMPO	Toluene	73
4	$AgNO_3$	BQ	TEMPO	Toluene	<5
5	$AgNO_3$	TBHP	TEMPO	Toluene	<10
6	$AgNO_3$	$K_2S_2O_8$	TEMPO	DMF	34
7	$AgNO_3$	$K_2S_2O_8$	TEMPO	CH_3CN	15
8	$AgNO_3$	$K_2S_2O_8$	TEMPO	CH_2Cl_2	<5
9	—	$K_2S_2O_8$	TEMPO	Toluene	0
10	$AgNO_3$	$K_2S_2O_8$	—	Toluene	<10
11	$AgNO_3$	—	TEMPO	Toluene	<10
12[c]	$AgNO_3$	$K_2S_2O_8$	TEMPO	Toluene	68

[a] Reaction conditions: styrene (0.3 mmol, 1 equiv.), diethyl *H*-phosphonates (1.5 equiv.), Ag salt (0.05 equiv.), oxidant (2 equiv.), TEMPO (0.4 equiv.) in toluene (2 ml) at 100 °C for 6 h. [b] Isolated yields. [c] Under a nitrogen atmosphere.

parameters further. After a series of trials of silver catalysts, we were pleased to find that the yield of vinylphosphonate could be improved up to 73% in the presence of 0.05 equiv. of $AgNO_3$. Analysis of the ^{1}H NMR of the final product indicated that the configuration of the double bond was *trans*, showing the reaction is highly stereoselective. Among the organic and inorganic oxidants examined, $K_2S_2O_8$ turned out to the best choice while the use of oxidants such as TBHP and benzoquinone gave very low yields (Table 1, entries 4 and 5). Subsequently, a number of solvents including toluene, DMF, CH_3CN and CH_2Cl_2 were examined, and tests revealed toluene to be the best solvent (Table 1, entries 3 and 6–8). The control reaction also indicated that the silver catalyst played a key role in the reaction and no desired product was formed in the absence of Ag catalyst (Table 1, entry 9). The yields are very low when either $K_2S_2O_8$ or TEMPO was absent, showing both oxidant and additive are indispensable for obtaining high yields (Table 1, entries 10 and 11). The reaction could be carried out under a nitrogen atmosphere, and **2a** was isolated in a slightly lower yield, showing that air is not essential for the reaction to proceed (Table 1, entry 12). On the basis of the above results, we decided to allow styrene to react with 1.5 equiv. of diethyl *H*-phosphonates with 5 mol% of $AgNO_3$, 2 equiv. of $K_2S_2O_8$ and 0.4 equiv. TEMPO in toluene at 100 °C as our standard conditions.

With the optimized conditions in hand, we next set out to examine the scope of *H*-phosphonates and styrenes, and the results are summarized in Table 2. A range of styrene derivatives were found to undergo dehydrogenative phosphonation in good to excellent yields ranging from 51–73% with high stereoselectivity. It is gratifying to see that our reaction not only worked with dialkyl *H*-phosphonates but also with diphenylphosphine oxide as well. Thus a series of vinylphosphine oxides were synthesized stereoselectively using our standard conditions in 53–81% yield (Table 2, entries **2n–2u**, **2w**, **2x**, **2af**). Substituents such as methyl, methoxy, ethoxy, *tert*-butyl, fluoro, chloro, bromo, iodo, cyano and acetyl groups are well tolerated on the aromatic ring and their reactions afforded the target products in good to excellent yields, showing

**Table 2** Silver-catalyzed carbon–phosphorylation of styrenes[a,b]

[a] Reaction conditions: styrene (0.3 mmol, 1 equiv.), diethyl *H*-phosphonates (1.5 equiv.), $AgNO_3$ (0.05 equiv.), $K_2S_2O_8$ (2 equiv.), TEMPO (0.4 equiv.) in toluene (2 ml) at 100 °C for 6 h. [b] Isolated yields.

the broad scope of this reaction. Styrenes with electron-donating groups could give slightly better yields than analogues with electron-withdrawing groups. Notably, sterically demanding substrates like 2,4,6-trimethylstyrene could be phosphorylated in 65% yield (**2h**). When the benzene ring of the substrates was changed to naphthalene, the reaction successfully provided the desired vinylphosphonate product **2i** in 68% yield.

We were pleased to find styrenes with a methyl group on the β-position can afford the corresponding (*E*)-vinylphosphonate **2v** and vinylphosphine oxide **2w** in yields above 50%. More impressively, α-methyl substituted styrene yielded the desired products **2x–2ab** in good to excellent yields as well. It is worthwhile to point out that, unlike the results reported by Maiti,[12c] only *E* products were obtained in all cases irrespective of the position of the methyl group (α or β). Under the standard conditions, cyclic olefins of different complexity also reacted smoothly to give **2ac**, **2ad** and **2ae** in good yields. In addition, a thiophene derivative could also afford the desired product **2af** in 64% yield. Unfortunately, the reactions of aliphatic olefins and conjugated dienes with diethyl *H*-phosphonate or phosphine oxides turned out to be messy.

Control experiments were designed to investigate the mechanism of this transformation. Since a pioneering report has shown that silver salts can react with $Ph_2P(O)H$ to form the corresponding active $Ph_2P(O)Ag$ complexes which subsequently generate the •$Ph_2P(O)$ radical,[14] we surmise that $Ph_2P(O)Ag$ may have played a critical role in our syntheses of vinylphosphine oxides. Indeed, when the $Ph_2P(O)Ag$ complex was used in a stoichiometric fashion in our reaction, the phosphorylated
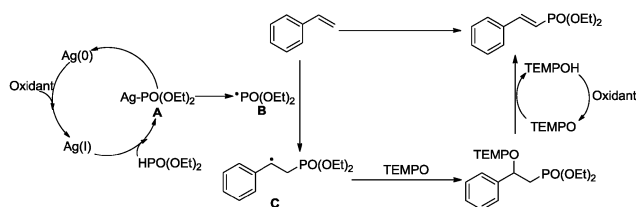
Scheme 1 Proposed reaction mechanism.

styrene was isolated in 72% yield. Thus, it is reasonable to assume a phosphoryl radical is an active intermediate in our reaction.

Based on this result and literature precedents,[12,14] the following plausible mechanism can be proposed for the transformation. The phosphoryl radical **B** may be generated from the complex **A** which itself is formed by the reaction of Ag catalyst with the phosphite under the reaction conditions. The resultant intermediate **B** subsequently adds to the styrene to form a carbon-centered radical **C** which was trapped by TEMPO to form intermediate **D**. With the assistance of another molecule of TEMPO, intermediate **D** undergoes elimination to form the desired vinylphosphonate product[12] and TEMPOH and Ag(0) could be oxidized back to TEMPO and Ag(I) by $K_2S_2O_8$, respectively, thus closing the catalytic cycle. The high *E*-selectivity observed with most products indicated that the reaction is a thermodynamically controlled process (Scheme 1).

In summary, we have developed a novel and highly stereo-selectivity protocol for the synthesis of vinylphosphonates and phosphine oxides starting from styrenes. This process features a broad substrate scope and excellent functional-group tolerance. The yields of the reaction are generally high and the reaction is very simple to run. Further studies on the clarification of the reaction mechanism and application to other substrates are underway and the results will be reported in due course.

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