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Direct Aryloxylation/Alkyloxylation of Dialkyl Phosphonates for the Synthesis of Mixed Phosphonates

Hai Huang,^[a] Johanna Denne,^[b] Chou-Hsun Yang,^[b] Haobin Wang,^[b] and Jun Yong Kang^{*[a]}

Abstract: The direct functionalization strategy of inertial dialkyl phosphonates with hydroxy compounds to afford diverse mixed phosphonates with good yields and functional group tolerance has been developed. Mechanistic investigations of both NMR studies and DFT studies support that an unprecedented highly reactive P(V) species (phosphoryl pyridin-1-ium salt), a key intermediate for this new synthetic transformation, is generated *in situ* from dialkyl phosphonate in the presence of Tf₂O/pyridine.

Organophosphonate compounds are ubiquitous structural motifs widely present in pharmaceuticals,^[1] agrochemicals,^[2] and ligand scaffolds^[3], highlighting the significance of these structures. Among them, mixed alkyl aryl phosphonates have attracted significant attention in nucleoside phosphonate prodrugs^[4] and in coordination chemistry for the study of biological system **A** (Figure 1).^[5] Mixed phosphonates show a wide range of biological activities such as phosphonate prodrugs of butyrophilin ligand **B**^[6] and antibacterial reagent **C**.^[7] They are also used as γ -glutamyl transpeptidase inhibitors **D**^[8] and esterase inhibitors **E**.^[9] Moreover, due to their unique structural properties of a hydrolysable P–O bond, mixed phosphonate units have been utilized as fluorogenic analogues to study biological mechanisms.^[10]

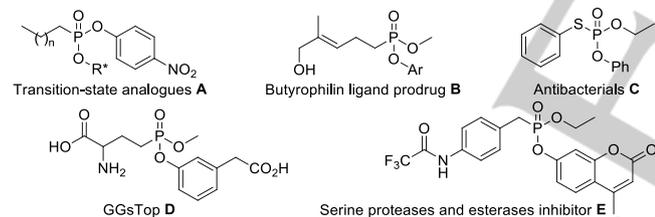
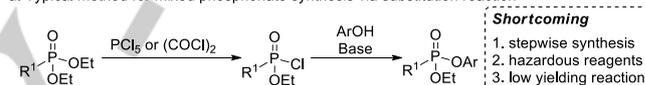


Figure 1. Examples of pharmaceutically-relevant mixed alkyl aryl phosphonates

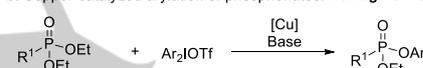
Current synthetic approaches toward mixed alkyl aryl phosphonates predominantly rely on stepwise processes involving substitution reaction of pre-generated alkyl phosphonochloridates with arenes (Scheme 1, a).^[6, 11] These methods employ hazardous and toxic reagents such as phosphorus chloride and oxalyl chloride to generate the

phosphonochloridates. In 2014, Feringa and co-workers^[12] disclosed an efficient copper-catalyzed direct arylation of dialkylphosphonates with diaryliodonium salts for the synthesis of mixed alkyl aryl phosphonates, which requires elevated reaction temperature and extra steps to prepare diaryliodonium salts (Scheme 1, b). Therefore, a direct aryloxylation/alkyloxylation of dialkylphosphonates in one-pot using phenols/alcohols under mild reaction conditions is an ideal and step-economic strategy to generate mixed phosphonates. However, there are several challenges: (1) as compared to the reactive phosphonochloridates, P(O)-H,^[13] and P(O)-OH compounds,^[14] the phosphonate moieties are chemically inert; (2) For the mixed phosphonate synthesis, the reactivity and chemoselectivity must be carefully controlled to prevent dual substitution of the twin alkoxy groups.

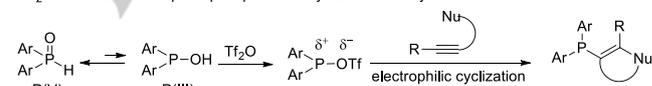
a. Typical method for mixed phosphonate synthesis via substitution reaction



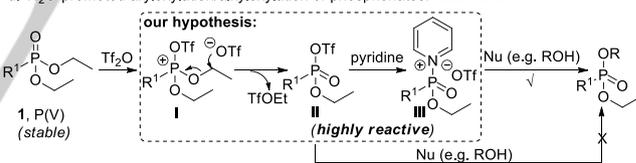
b. Copper-catalyzed arylation of phosphonates: **Feringa's work**



c. Tf₂O-mediated electrophilic phosphination/cyclization of alkynes: **Miura's work**



d. Tf₂O-promoted aryloxylation/alkyloxylation of phosphonates: **this work**



Scheme 1. Synthetic routes toward mixed phosphonates

Triflic anhydride (Tf₂O)-mediated activation of carbonyl compounds such as ketones, aldehydes, and amides as well as sulfoxides has emerged as a powerful synthetic tool in organic synthesis.^[15] Similarly, the activation of phosphorus compounds with P=O bond, especially phosphine oxides, was also achieved by Tf₂O.^[16] Recently, Miura and co-workers^[17] reported an elegant strategy for the activation of *H*-phosphine oxides. An electrophilic phosphorus species (P-species) generated from a diaryl phosphine oxide and Tf₂O reacts with an alkyne to form a reactive phosphirenium cation, which undergoes arylative ring-opening reaction to afford phosphinative cyclization product. (Scheme 1, c). Despite the demonstration of electrophilic P-species from the secondary arylphosphine oxides and Tf₂O at elevated temperature,^[17-18] the activation of dialkylphosphonates with Tf₂O at room temperature to generate electrophilic P-species remains undeveloped. Hence, we hypothesized that the terminal oxygen P(V)=O of dialkylphosphonates **1** could be activated by Tf₂O to afford a phosphoryl pyridinium intermediate **I** (Scheme 1, d),^[19] which is then converted to TfO-substituted phosphonate intermediate **II** *via*

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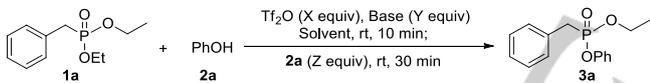
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nucleophilic substitution reaction.^[20] Finally, we envisioned that the phosphonate intermediate **II** in presence of pyridine could be transformed to a highly reactive pyridinium phosphonate intermediate **III**.^[21] With this idea in mind, we explored the development of new electrophilic P-species using the chemically inert dialkylphosphonates for a facile synthesis of mixed phosphonates. Herein, we describe metal-free, chloride reagent-free, and Tf₂O-mediated activation of phosphonates for the synthesis of mixed phosphonates *via* direct aryloxylation/alkyloxylation strategies.

Optimization of the reaction conditions was carried out with diethyl benzylphosphonate **1a** and phenol **2a** (see the Supporting Information for the initial works). Initially, we studied pre-activation time for the generation of the intermediate **III** shown in Scheme 1 (d), and we found that a pre-reaction time of 10 min prior to the addition of **2a** to a mixture of **1a** and Tf₂O/pyridine is required for high yields (Table 1, entry 1). Screening of other bases did not improve the product yield but a phenyl triflate byproduct was formed (See SI for details). In contrast, there was no target product without bases (Table 1, entry 2). Among the screened solvents, DCM is superior to other solvents (Table 1, entries 3-8). Further optimization revealed that the highest yield of **3a** (99% yield by NMR) could be achieved with an excess of Tf₂O (1.5 equiv), pyridine (2.0 equiv), and phenol **2a** (2.5 equiv) (Table 1, entry 9, See SI for details).

Table 1. Optimization of reaction conditions^[a]



entry	base	solvent	X:Y:Z	yield (%) ^[b]
1	pyridine	DCM	2.0:2.0:2.0	85
2	–	DCM	2.0:2.0:2.0	NR
3	pyridine	CHCl ₃	2.0:2.0:2.0	37
4	pyridine	DCE	2.0:2.0:2.0	49
5	pyridine	Et ₂ O	2.0:2.0:2.0	46
6	pyridine	toluene	2.0:2.0:2.0	36
7	pyridine	THF	2.0:2.0:2.0	NR
8	pyridine	CH ₃ CN	2.0:2.0:2.0	trace
9	pyridine	DCM	1.5:2.0:2.5	99(92) ^[c]

[a] Reaction conditions: **1a** (0.2 mmol), Tf₂O (X equiv), base (Y equiv) in solvent (1.0 mL) for 10 min, then PhOH (Z equiv) for 30 min. [b] Yield was determined by ¹H NMR on the crude reaction mixture using 1,3,5-trimethylbenzene as an internal standard. [c] Isolated yield.

With the optimized reaction conditions in hand, the scope of the reaction was explored with diverse dialkyl phosphonates **1**, demonstrating efficient substrates to form mixed alkyl aryl phosphonates **3a-3x** (Scheme 2). Different substituents on the benzyl group were well tolerated (86-94% yields) (Scheme 2, **3a-3g**). Phosphonates with aliphatic substituents **1h-1j** are also suitable substrates for this reaction to provide alkyl-substituted mixed phosphonates **3h-3j** in 85-90% yields. In addition, phenyl phosphonates **1k-1n** with different alkoxy substituents MeO, EtO, *i*-PrO and *n*-BuO were examined, and they afforded the corresponding mixed phosphonates **3k-3n** in 81-93% yields. In line with our hypothesis of favoring electron-rich substituents on the phosphonate motif for the activation with Tf₂O, the electronic

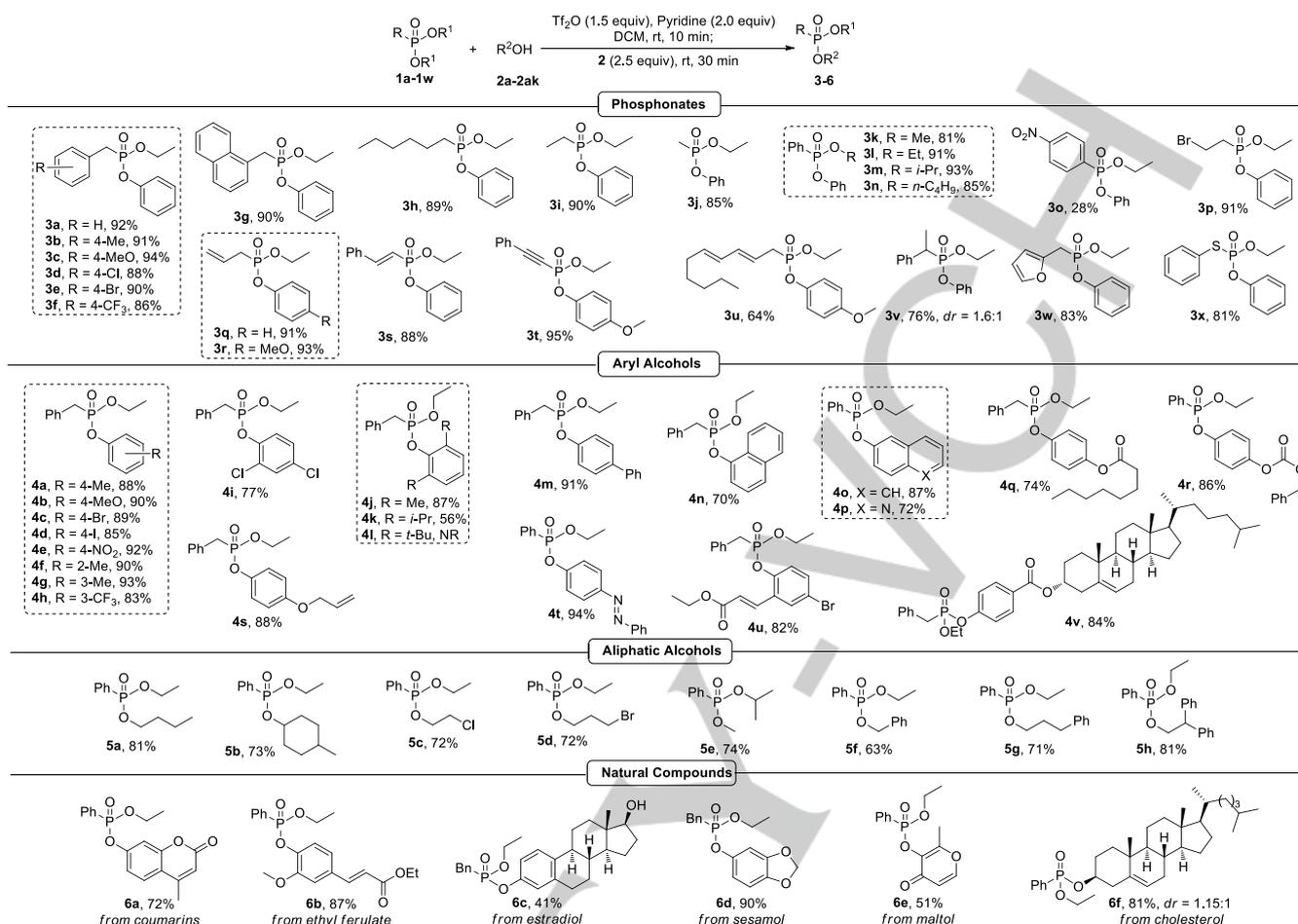
effects of the phenyl substituents on the phosphonates have significant influence on the product yield: for example, an electron-deficient phosphonate **1o** with a *p*-nitro phenyl substituent provided the product **3o** in 28% yield (Scheme 2). This reaction shows broad compatibility with a diverse array of substrates bearing halide, allylic, vinyl, alkyne, and diene groups (Scheme 2, **3p-3v**). A heteroaromatic phosphonate was also efficiently transformed to the desired mixed phosphonate **3w** in 83% yield. Importantly, the synthesis of *O*-ethyl *O*-, *S*-diphenyl phosphorothioate **3x** known as a classical antibacterial agent^[7] was demonstrated by this system with 81% yield.

We next investigated the scope of phenol derivatives. The reaction tolerates both electron-donating groups (Me, MeO) and electron-deficient substituents (Br, I, NO₂, CF₃) on the phenyl ring, providing the desired products in high yields (Scheme 2, **4a-4h**). *Ortho*-, *para*-substituted dichlorophenol was a suitable substrate for this transformation to afford **4i** in 77% yield. In contrast, having bulky groups on 2-, 6-positions on phenols significantly reduced the product yields (Scheme 2, **4k-4l**). To our delight, as compared to our initial experimental results with no pre-activation process (see Table S1 in SI), polycyclic aromatic alcohols such as 1-naphthol, 2-naphthol, and quinolin-6-ol proved to be suitable substrates under our optimized reaction conditions, affording the mixed phosphonates **4n-4p** in 70-87% yields. In addition, this method tolerates a wide range of functional groups (e.g., ester, carbonate, allyl, azo and acrylate) on the phenol (Scheme 2, **4q-4u**). Especially, the reaction of **1a** with cholesterol-derived phenol proceeded efficiently to give **4v** as a phosphorylated cholesteryl ester derivative bearing a biologically important mixed phosphonate scaffold in 84% yield (Scheme 2, **4v**).

With a demonstration of aryloxylation of phosphonates with various phenol derivatives, we next explored the reactivity of aliphatic alcohols under the same reaction conditions (Scheme 2). We found that various alcohols such as 1° alcohols and 2° alcohol were all efficiently coupled with dialkylphosphonates to provide mixed phosphonates **5a-5h** in moderate to high yields.

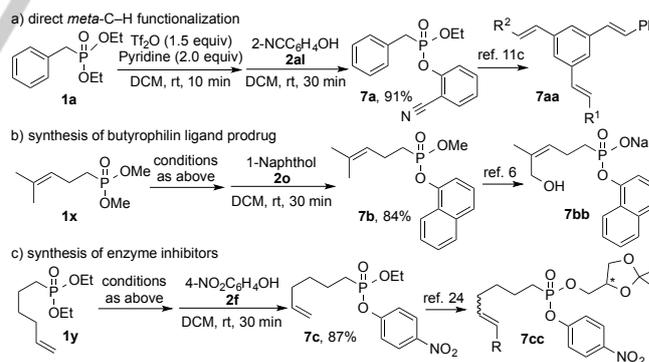
Next, we investigated late-stage phosphorylation of various natural products to demonstrate functionalization of bioactive small molecules (Scheme 2). This phosphorylation reaction of natural compounds such as coumarin **2af**, ferulate **2ag** and estradiol **2ah** exhibited good functional group tolerance (e.g. ester, acrylate, ether, and hydroxyl group) and provided the corresponding products in moderate to high yields (Scheme 2, **6a-6c**). It is worth mentioning that this protocol shows an excellent chemoselectivity with estradiol **2ah** bearing both aryl alcohol and aliphatic alcohol, providing only **6c** with 41% yield. In addition, sesamol **2ai** afforded the corresponding mixed phosphonate **6d** in excellent yield (90% yield). An enol nucleophile of maltol was also a suitable coupling partner for this transformation to furnish the desired mixed phosphonate **6e** in 51% yield. Finally, we subjected an aliphatic alcohol-containing natural product cholesterol **2ak** to our standard reaction conditions, and we isolated the target mixed phosphonate product **6f**^[22] with 81% yield.

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Scheme 2. The reaction scope. For the standard reaction conditions, see supporting information. Isolated yields are given.

To demonstrate the potential application of this synthetic protocol to pharmaceuticals and organic synthesis, we performed a larger-scale reaction of **1l** (1.07 g, 5.0 mmol) with **2a**, which afforded the target mixed phosphonate **3l** (1.26 g) in 96% yield along with 52% recovery of the phenol **2a** (See SI for details). 2-Hydroxybenzonitrile **2al** was also a suitable substrate and generated a functionalized phosphonate **7a** (87% yield), which is a key precursor for *meta*-C–H activation of the benzene ring to give multi-substituted benzene compounds **7aa** (Scheme 3, a).^[11c, 23] Next, we applied our aryloxylation protocol for the synthesis of a key intermediate of butyrophilin ligand prodrug **7bb** reported by the Wiemer group. Our transformation achieved one step synthesis of **7b** from **1x** and **2o** and enables higher yield (84%) in short reaction time (40 min) (Scheme 3, b).^[6] Finally, a mixed phosphonate **7c**, a key intermediate of polymer immobilized enzyme inhibitors **7cc**, was also successfully synthesized in 87% yield from **1y** and **2f** (Scheme 3, c).^[24]

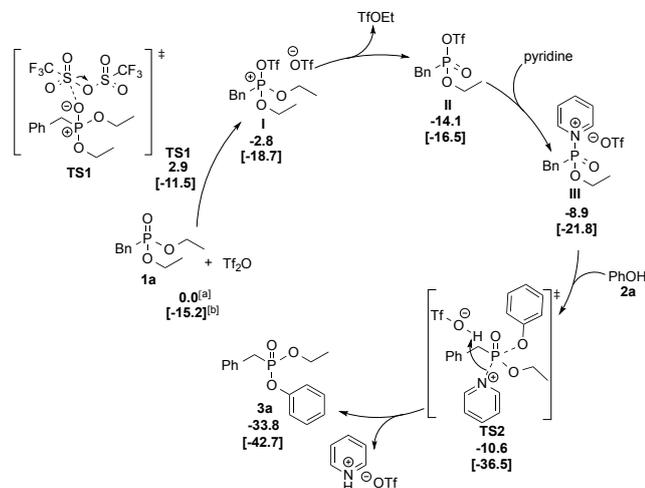


Scheme 3. Larger-scale reaction and synthesis of key mixed phosphonates as versatile building blocks

Based on the experimental data and density functional theory (DFT) calculations (See SI for details), a plausible mechanism is proposed in Scheme 4. The terminal oxygen of the phosphonate **1a** attacks the Tf₂O via **TS1** to furnish a phosphonium intermediate **I**. Next, TfO-substituted phosphonate **II** and ethyl triflate byproduct are generated via S_N1-type mechanism from the intermediate **I**.^[12, 25] Then, the pyridine nucleophile attacks the

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intermediate **II** to form a highly reactive electrophilic phosphorus species of phosphoryl pyridin-1-ium **III**.^[26] Finally, this intermediate **III** is transformed to the mixed phosphonate **3a** by substitution reaction with phenol **2a** through the **TS2**.^[21b, 21c, 27]



Scheme 4. Proposed mechanistic pathway. Theoretical investigations on the reaction pathways for the formation of **3a**. Free energy (ΔG) and enthalpy corrections (ΔH) of key intermediates and transition states are obtained at the DFT-M062X/6-31G*/MP2/6-311++G**/PCM(DCM) level of theory; [a] ΔG (298K, in kcal/mol); [b] ΔH (298K, in kcal/mol).

In summary, we have developed a mild, efficient, direct aryloxylation/alkyloxylation of dialkyl phosphonates for the synthesis of mixed phosphonates. This synthetic transformation enabled the synthesis of a wide range of functional mixed phosphonates without the use of metal or chloride reagents. In this chemistry, we have demonstrated that a phosphoryl pyridin-1-ium, a highly electrophilic P-species of powerful phosphorylation reagent for the synthesis of mixed phosphonates, can be generated from dialkyl phosphonates with Tf_2O /pyridine. The synthetic utility of this transformation was demonstrated by the synthesis of key intermediates of bioactive compounds (butyrophilin ligand prodrug and enzyme inhibitors) and the late-stage phosphorylation of natural compounds.

Experimental Section

Ethyl phenyl benzylphosphonate (3a): To a solution of diethyl benzylphosphonate **1a** (45.4 mg, 0.2 mmol), Tf_2O (50.5 μL , 0.3 mmol) in DCM (1.0 mL) was added pyridine (32 μL , 0.4 mmol) in a 2-dram vial with a PTFE cap. After stirring for 10 min, phenol **2a** (46.5 mg, 0.5 mmol) was added to the reaction mixture. After stirring for another 30 min at room temperature, the resulting mixture was concentrated to give the crude product which was then purified by column chromatography on silica gel to afford ethyl phenyl benzylphosphonate (**3a**): 50.8 mg, 92%; as a colorless oil.

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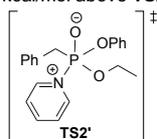
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Keywords: Aryloxylation • Alkyloxylation • Phosphonates • Phosphoryl pyridin-1-ium • DFT study

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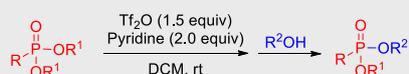
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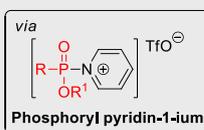


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Direct functionalization strategy of inertial phosphonates

Broad scopes: more than 60 examples, up to 94% yield
Mild conditions: Metal-free, toxic chloride reagent-free
Mechanism understanding: *in situ* NMR study and DFT study
Potential applications: including late-stage phosphorylation



Hai Huang, Johanna Denne, Chou-Hsun Yang, Haobin Wang, Jun Yong Kang*

Page No. – Page No.
Direct Aryloxylation/Alkyloxylation of Dialkyl Phosphonates for the Synthesis of Mixed Phosphonates

We expanded the applicability of Tf_2O to phosphorus chemistry for generating electrophilic P-species and developed a novel metal-free activation strategy of stable dialkyl phosphonates for the synthesis of diverse mixed phosphonates.