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FULL PAPER

Direct Enamido C(sp^2)-H Diphosphorylation Enabled by PCET-triggered Double Radical Relay: Access to *gem*-Bisphosphonates

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Abstract: Here we report a novel and straightforward protocol for the construction of valuable *gem*-BPs by means of proton-coupled electron transfer (PCET)-triggered enamido C(sp^2)-H diphosphorylation. This reaction represents a rare example of realizing the challenging double C-P bond formation at a same carbon atom, thus providing facile access to a broad variety of structurally diverse bisphosphonates from simple enamides under silver-mediated conditions. Initial mechanistic studies demonstrated that the diphosphorylation involves two rounds of PCET-initiated radical relay process.

Introduction

Geminal bisphosphonates (*gem*-BPs) are an important class of compounds possessing the unique P-C-P moiety, and they are stable analogues of naturally-occurring pyrophosphate (Figure 1).[1] Owing to their gifted bone affinity and specific inhibition for FPPS (farnesyl pyrophosphate synthase), *gem*-BPs are currently the most commonly used medicines in a variety of bone-relevant diseases.[2] For instance, among them are several renowned anti-osteoporosis drugs including clodronate, pamidronate, and residronate (Figure 1, top).[3] Particularly, nitrogen-containing *gem*-BPs have emerged as a significant type of highly potential candidates to kill tumor cells for prevention and therapy of a series of human cancers, and thus draw great interest in the past decade.[4] However, their practical use for anticancer therapeutic agents is often hampered due to poor cellular uptake, so there has recently been considerable interest in developing more lipophilic *gem*-BPs, as exemplified by representative solutions such as replacing the hydroxyl "bone hook" at the geminal carbon with simple hydrogen or lipophilic fluorine atom, introducing a long carbon chain, or masking the negatively charge with pivoxil esters (Figure 1, middle).[5] Beyond the important pharmacological roles, *gem*-BPs have also been comprehensively exploited in biomedical fields owing to their reliable metal-chelating ability.[6] For example, the bone-seeking property of *gem*-BPs provides promising opportunity to deliver medical targets specifically to bone by versatile bisphosphonate conjugations

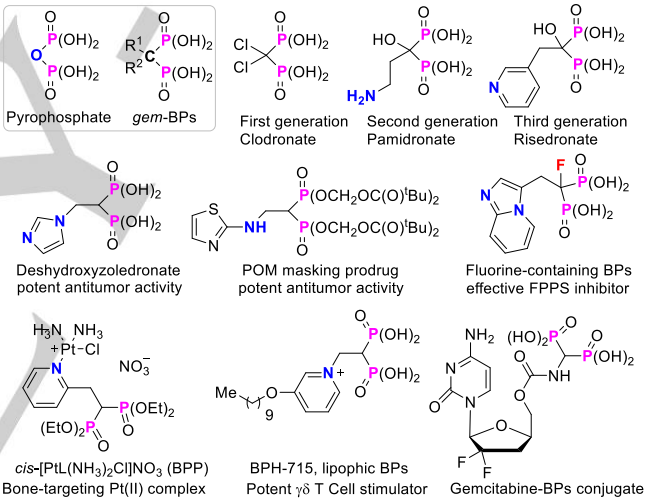

Figure 1. Representative biologically important molecules containing *gem*-bisphosphonates.

(Figure 1, bottom).[7] Despite these impressive advances in *gem*-BPs' biological studies, the scarcity of reliable synthetic methods to expand the structural diversity of *gem*-BPs has become the major limiting factor of the impetus. Indeed, the majority of conventional approaches mainly focused on the preparation of α-hydroxyl or α-amino bisphosphonates (Scheme 1a).[8] Alternatively, ionic C-C bond-forming transformations with bisphosphonate building blocks, such as vinylidenebisphosphonate ethyl ester (VBP)[9] and methylene-bisphosphonate ethyl ester (MBP),[10] have proved to be valid route to produce lipophilic *gem*-BPs (Scheme 1b), but the utility is still largely restricted due to limited substrate scope, poor selectivity, and tedious pre-synthesis of the bisphosphorous reagents. In particular, the synthesis of tetra-substituted vinyl *gem*-BPs has not been reported until now.[11] Therefore, the development of general and efficient synthetic methods to rapidly

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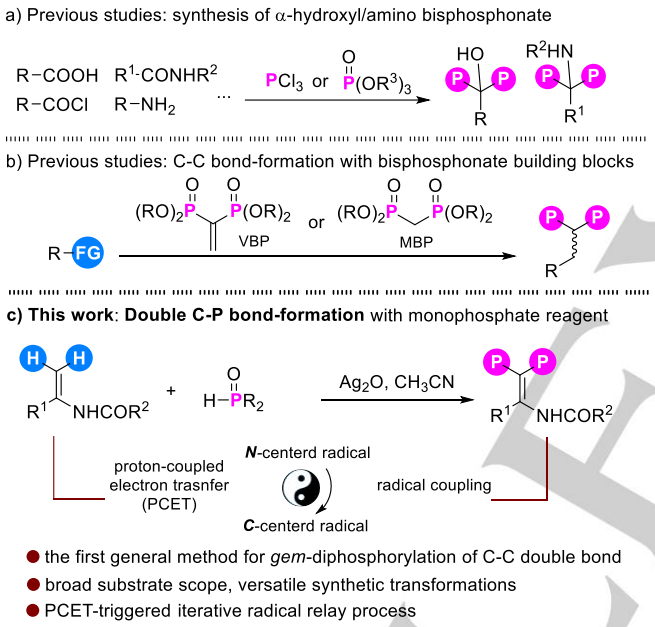
produce versatile functionalized *gem*-BPs from simple chemical entities is still highly desirable.

C-H phosphorylation has been recognized as a straightforward approach to produce various organophosphorus compounds.[12] Although powerful, all the precedented examples only focus on mono-phosphorylation, while the more attractive C-H diphosphorylation has not been realized until now, especially 1,1-diphosphorylation at a same carbon atom.[13] Herein, we report a major advance for synthesizing geminal bisphosphonates by means of silver-mediated direct 1,1-diphosphorylation of enamides (Scheme 1c).[14] By taking advantage of proton-coupled electron transfer (PCET)[15]-triggered radical relay process,[16] this study implemented the first example of two-fold C-P bond formation from C(sp^2)-H bond at a same carbon atom.[17] More importantly, this reaction allows the efficient synthesis of a broad range of fully functionalized β-amino vinyl *gem*-BPs, as well as halogen, azirine, ketone, peptide, and alkyne-substituted ones, thus considerably opening up new possibilities in expanding the potential chemical space in this emerging field.



Scheme 1. Development of general synthetic means for the construction of *gem*-bisphosphonates.

Results and Discussion

Extensive screening of various reaction parameters (see the SI for details) concluded that the desired β-amino vinyl *gem*-bisphosphonate **3a** was afforded in 84% yield when phenyl enamide **1a** was reacted with diisopropyl phosphonate **2a** in the presence of silver oxide (Ag_2O) at reflux for 12 h in acetonitrile. The employment of Ag_2O plays a critical role in this transformation, as evidenced by the fact that almost no conversion was observed when using other metal complexes [such as $Mn(OAc)_3$] or silver salts (including AgF, AgOAc, $AgNO_3$, Ag_2SO_4, and Ag_2CO_3). Moreover, attempts to reduce the amount of Ag_2O turned out to be unworkable, suggesting that the silver reagent may bear multiple roles in the reaction process (*vide infra*). The substrate scope of this C(sp^2)-H diphosphorylation reaction was then evaluated under the optimized conditions (Scheme 2). For different phosphonate reagents, such as diethyl or dibutyl phosphonates, and diphenylphosphine oxide, the corresponding *gem*-bisphosphontaes **3b**–**3d** were smoothly afforded in 70–82% yields. Subsequently, enamide counterparts bearing a series of different amino-protecting groups, including isopropyl, tert-butyryl, benzoyl, and benzyloxycarbonyl, were all evaluated under the standard conditions, and gave rise to the products **3e**–**3h** in moderate to high yields. As for aryl enamides, this transformation could tolerate both electron-donating and electron-withdrawing substituents, such as -Me, -OMe, -halogens, -OCOMe, $-CF_3$, -CN, and $-CO_2Me$, irrelevant of their locating patterns on the phenyl ring, thus delivering the desired β-amido vinyl bisphosphonates **3i**–**3e'** in 61–88% yields. Notably, compound **3v** was analyzed with single X-ray to unambiguously determine the molecular structure, and other bisphosphonates are assigned by analogy.[18] Furthermore, the generation of compound **3m** possessing a long alkyl chain in practical yield displays the potential utility of this method in preparing lipophilic *gem*-BPs aiming for increased biological activities. 2-naphthyl enamide was found to be suitable reaction partner in this process (**3e'**). *N*-heterocycle-containing bisphosphonates have emerged as the third-generation candidates in searching for more effective drugs to treat bone-related diseases.[2,4] In this context, a wide array of pyrrole, thiophene, thiazole, pyridine, and *para*-diazine-derived enamides were prepared and reacted with phosphonate **2a** under identical conditions. Pleasingly, the corresponding *gem*-BPs **3f'**–**3o'** were readily provided in 61–81% yields, thereby allowing new possibilities in achieving structurally diversified bisphosphonates. In addition, alkyl-substituted enamides also proved to be applicable in this protocol, furnishing **3p'** and **3q'** in decent yields.[19] Ultimately, commercially available 2-acetamidoacrylates and *N*-vinylacetamide were treated with phosphonate **2a** under the optimal conditions, and produced highly functionalized α-dehydroamino acids and β-dehydroamino phosphoric acids derivatives **3r'**–**3t'** in 51–62% yields, providing another clear benefit of this facile protocol.

To demonstrate the scale-up feasibility of this diphosphorylation method, three representative examples (**3a**, **3d**, and **3k'**) were prepared in gram-scale, all observed with maintained good level of results compared with model reactions (Scheme 3a). In particular, the reaction between enamide **1a** and phosphonate **2a** was also operated at a scale of 10 grams, thus leading to 21.9 grams of **3a** in 75% yield in just 12 hours. It should be noted that excess Ag_2O and the remaining silver residue could be recycled by simple operations (Scheme 3b).[20] The reproduced Ag_2O could still facilitate the diphosphorylation with good activity, thus significantly improving the advantage of economic practicality. The immense value of P-C-P skeleton has been extensively demonstrated through its frequent presence in various active pharmaceutical ingredients, but available methods to achieve the structural diversity is still far from trivial. In this context, a diverse array of synthetic transformations with the obtained *gem*-BPs was further investigated. As illustrated in Scheme 3c, the free amino bisphosphonates [**4a** (X-ray confirmed) and **4b**] and carbonyl bisphosphonates [**6a** (X-ray confirmed) and **6b**] were smoothly provided in good yields under simple basic and acidic conditions, respectively.[18] More importantly, the azirine-functionalized *gem*-BPs **5a** and **5b** were afforded in high yields via I_2-mediated cyclization, thus adding another attractive handle to the central P-C-P motifs.

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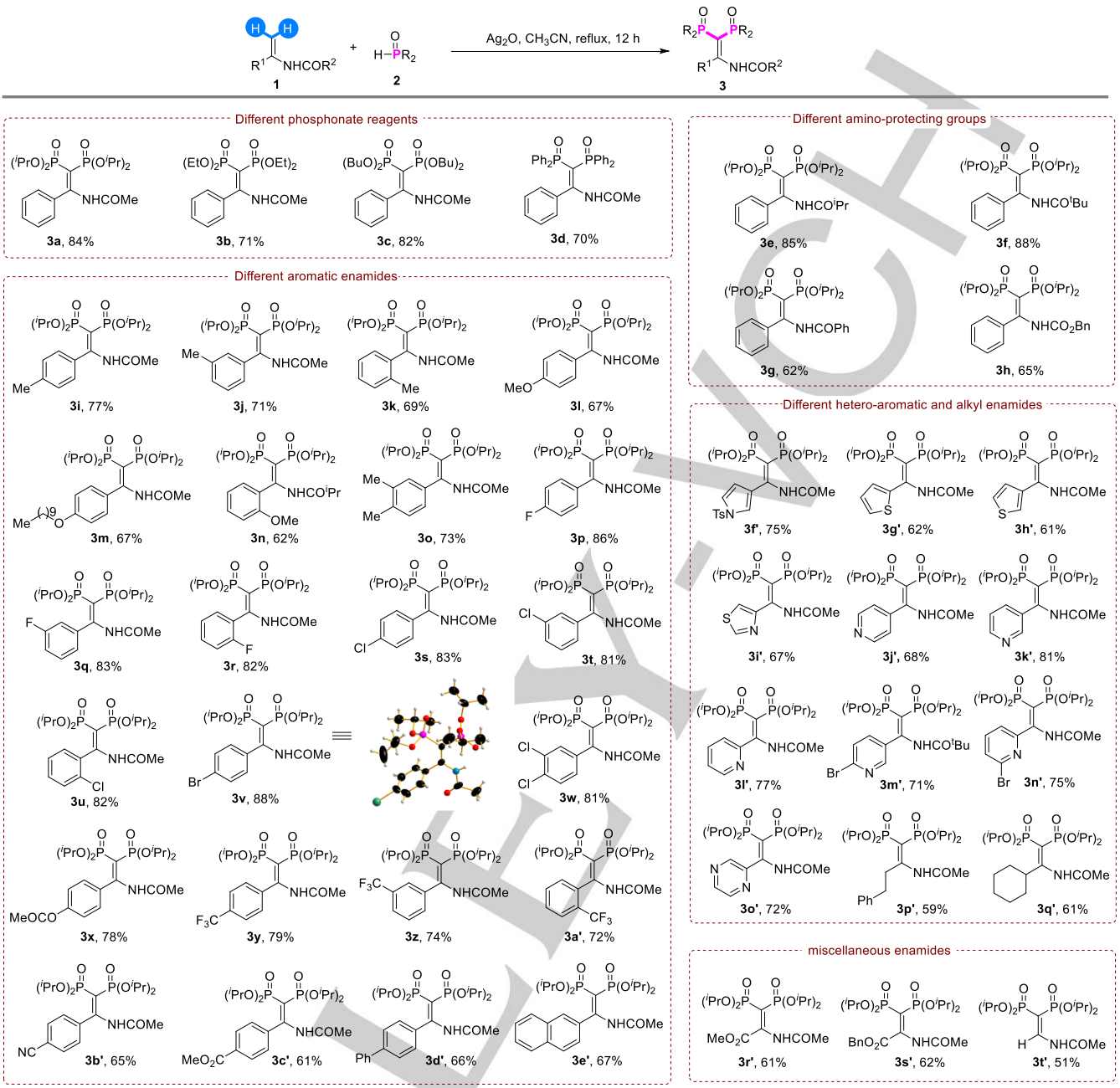

Scheme 2. Substrate scope of silver-mediated direct *gem*-diphosphorylation of enamides. Reaction conditions: A mixture of enamide **1** (0.5 mmol), H-phosphonate **2** (1.1 mmol) and Ag_2O (348 mg, 1.5 mmol) in CH_3CN (10 mL) was reacted at reflux temperature for 12 hours; Yield of isolated product.

Furthermore, a series of halogen-substituted bisphosphonates **7a**–**7d**, including -Cl, -Br, and -F, were all readily prepared by means of electronic substitution transformations. Among them, noteworthy is that the pyridine-containing compounds **6b** and **7d** represent the dehydroxyl and fluorinated analogues of Risedronic acid (drug for Paget's disease), respectively. Notably, the free bisphosphoric acid **6c** was obtained in 84% yield by simple treatment of **6a** with TMSBr. In addition, the practical applicability is exemplified by the rapid preparation of several pharmaceutical-relevant molecules with good efficiency, including **3u'**-*gem*-BPs-functionalized Celestolide derivative, **3v'**-*gem*-BPs-functionalized Gemfibrozil derivative, and **3w'**-an analogue of Pregnane X receptor agonist SR12813 (Scheme 3d).[21]

The presence of ester and amino groups in obtained BPs may offer new opportunity for connecting to medically relevant targets. As a proof of concept, the free acid-containing bisphosphonate **8a** was synthesized from compound **3s'** in good yield, and subsequently coupled with phenylalanine to give peptide-functionalized molecular **8b** in 75% yield (Scheme 4a). More importantly, we were pleased to find that the alkyne moiety could also be easily introduced to free amino-BPs **4**, thus allowing facile click ligation of **9a**–**9c** with Azidothymidine to give corresponding triazole-connected BPs **10a**–**10c** in high yields (Scheme 4b).

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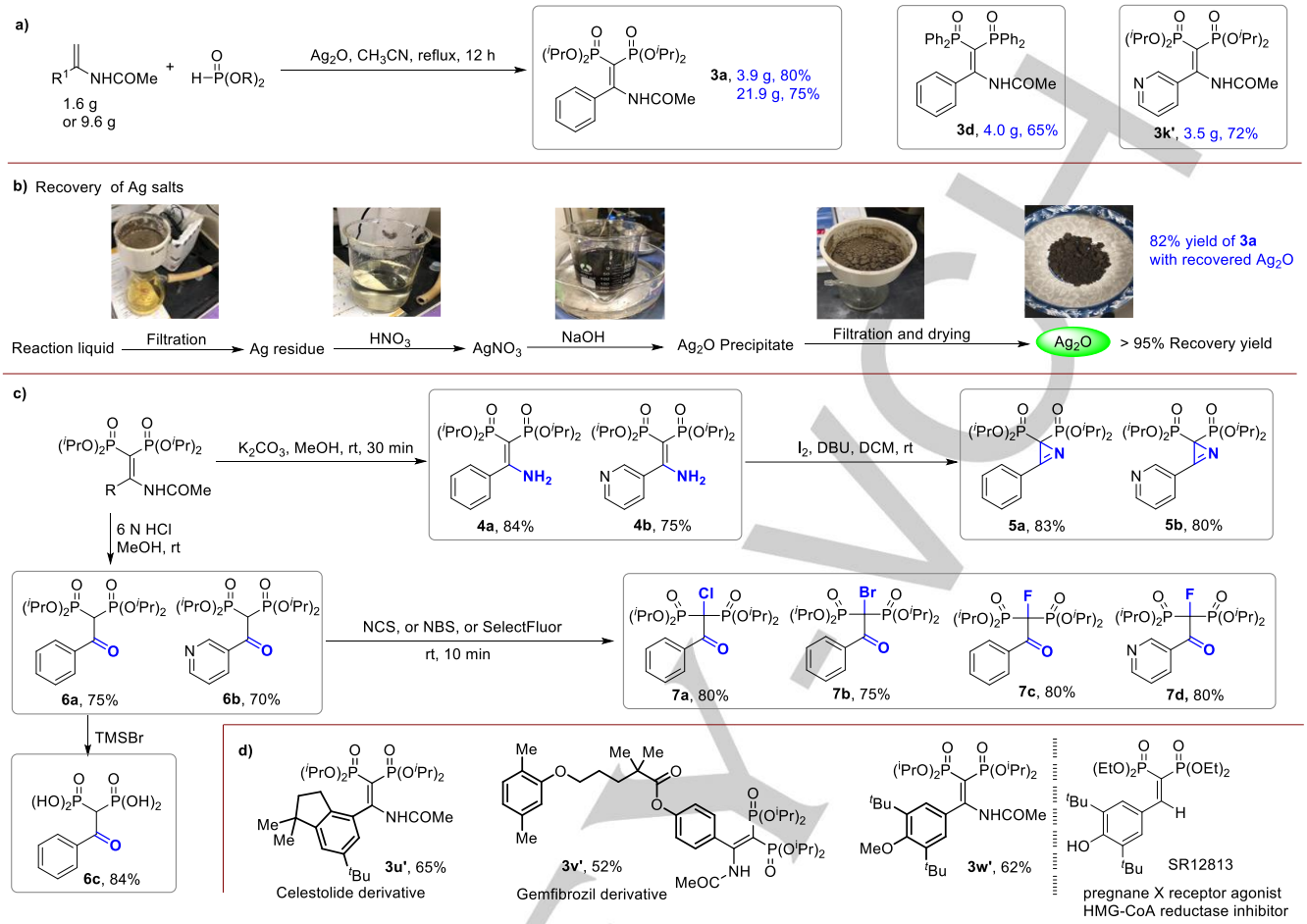
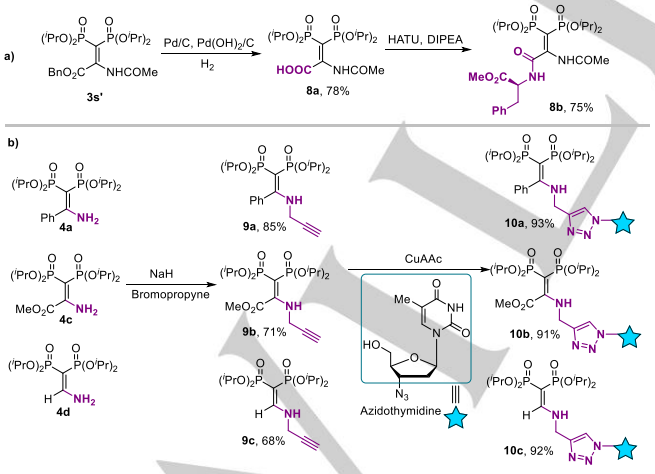


Scheme 3. Scale-up experiments and further synthetic transformations.



Scheme 4. Connections of amino-BPs to phenylalanine and Azidothymidine.

A series of experiments were subsequently conducted to cast some light on the mechanism of this novel *gem*-diphosphorylation reaction. Monitoring the reaction by ^{31}P-NMR and TLC suggested that it may first undergo mono-phosphorylation and then completed the reaction after the second C-P bond formation (see the SI for details). Indeed, both isomers of mono-phosphorylation intermediates *Z*-**11a** and *E*-**11a** were uneventfully converted to bisphosphonate **3a** in excellent yields (Scheme 5a). Remarkably, an isomerization process of the C-C double bond was observed during mechanistic studies.[22] For instance, the reaction between *Z*-**11a** and diphenylphosphine oxide provided **3x'** in 65% yield, whose stereochemistry has been confirmed by X-ray crystallographic analysis. Subsequently, a group of *N*-protected enamides, including -Me, -Bn, and -Boc, were prepared and subjected to otherwise identical reaction conditions, while only the mono-phosphorylation products **11b**–**11d** were formed in distinctly low yields (Scheme 5b). Reacting **11b**–**11d** with phosphonate reagent in a separated manner also turned out to be no conversion at all. These results strongly suggest that the N-H moiety may operate an essential role in initiating the reaction, especially for the second C-P bond formation. The addition of a radical scavenger (TEMPO) completely inhibited the diphosphorylation (Scheme 5c). Notably, both radical-trapping products **12a** and **12b** (X-ray confirmed) were obtained in a yield of 45% and 67%, respectively.[23] These results clearly demonstrate that the reaction could undergo in radical manner and *in-situ* generated alkyl radical species might account for the observed high reactivity of double C-P bond

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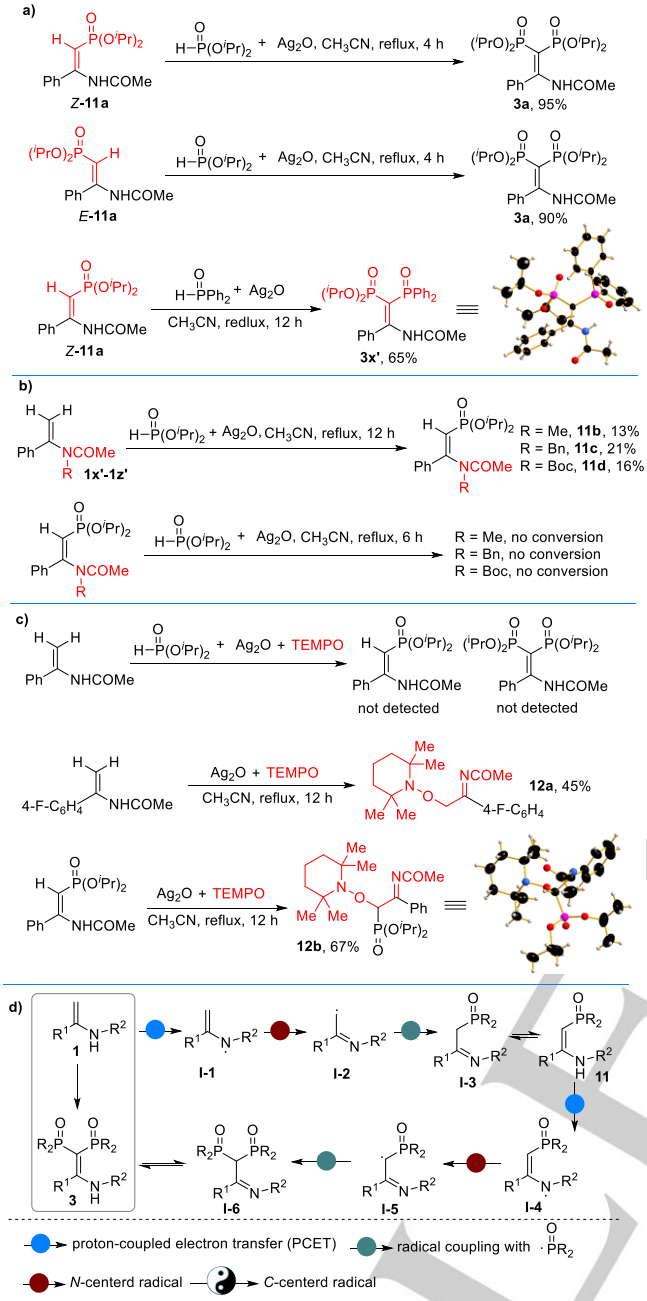

Scheme 5. Mechanistic studies and proposed mechanism.

formation. Collectively, a plausible mechanism is depicted in Scheme 5d based on the experimental clues and previous precedents. In the presence of Ag_2O, enamide **1** undergoes proton-coupled electron transfer (PCET) process to give amidryl radical **I-1**.[24] The silver oxide functions as both a mild oxidant and a weak Brønsted base during this step, thereby explaining its unique match for this transformation.[25] Then the *N*-centered radical would quickly isomerize to a more stable *C*-centered radical **I-2**.[26] At this stage, radical coupling between alkyl radical **I-2** and the *in-situ* formed *P*-centered radical gave rise to imine intermediate **I-3**.[27] Isomerization of **I-3** to mono-phosphorylation product **11** is driven by the formation of intramolecular hydrogen bond.[28] Likewise, a second round of radical relay process consisting of PCET, radical transfer, and radical coupling, would occur and accomplish another C-P bond formation, thus ultimately providing the final *gem*-bisphosphonate product **3**. It should be noted that this study represents the first example to successfully utilize PCET process for double C-H functionalization.

Conclusion

In summary, a novel method for the efficient preparation of valuable *gem*-bisphosphonates from readily accessible enamides is described. The realization of this transformation hinges on silver-mediated radical relay process involving PCET as the key step, thus solving the challenging double C-P bond formation at a same carbon atom. The good functional group compatibility and versatile synthetic transformations render the facile preparation of a wide range of highly functionalized gem-bisphosphonates under mild conditions. Given the enormous significance of the P-C-P backbones in biological and medical applications, the present protocol will open up new possibilities in relevant fields.

Experimental Section

General procedure for silver-mediated direct diphosphorylation of enamides. The mixture of enamide **1** (0.5 mmol, 1.0 equiv), Ag_2O (1.5 mmol, 3.0 equiv), and H-phosphonate **2** (1.1 mmol, 2.2 equiv) in CH_3CN (10.0 mL) were added into a 25 mL schlenk flask equipped with a stirring bar. The reaction was stirred at reflux temperature for 12 hours and monitored by TLC. Then the reaction mixture was filtered through diatomite (Put a layer of filter paper on the diatomite, and a silver residue filter cake will be formed on the filter paper. Collect the silver residues for regeneration and recycling). The filtrate was concentrated under reduced pressure and subsequently purified by flash column chromatography on silica gel with PE/EtOAc mixture (10/1–1/1 ratio). After removing the solvent in *vacuo*, the desired compound **3** could be obtained.

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Keywords: radical relay • bisphosphonates • enamides • silver • synthetic methods

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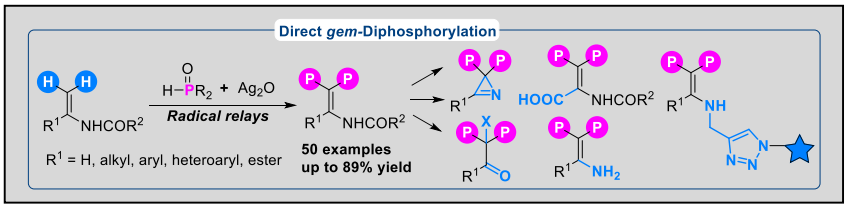

Direct double C-P bond formation at a same carbon atom in one-pot: By taking advantage of PCET-triggered radical relay process, a new general method to versatile valuable functionalized *gem*-bisphosphonates is described.

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