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Silver-Promoted Direct Phosphorylation of Bulky C(sp^2)–H Bond to Build Fully Substituted β-Phosphonodehydroamino Acids

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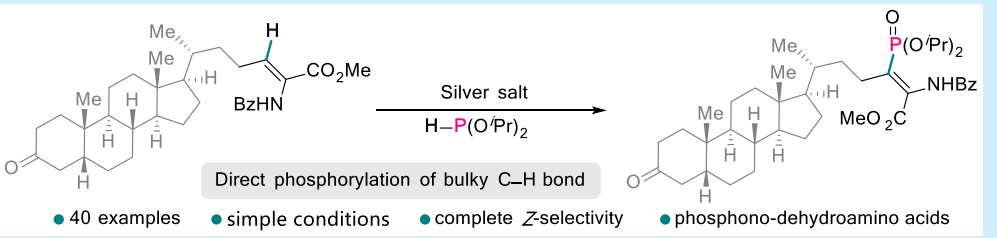

ABSTRACT: A general and practical cross-dehydrogenative coupling protocol between readily available trisubstituted α,β-dehydro α-amino carboxylic esters and H-phosphites is described. This C(sp^2)–H phosphorylation reaction proceeds with absolute *Z*-selectivity promoted by silver salt in a radical relay manner. The bulky tetrasubstituted β-phosphonodehydroamino acids were obtained in grams and added new modules to the toolkit for peptide modifications.

Unnatural amino acids such as α,β-dehydroamino acids (dhAAs) do not belong to the 20 canonical proteinogenic amino acids, yet they are found widespread in natural products and play a very important role in pharmaceutical science (Figure 1).[1] The unique polar double bond endows dhAAs with increased structural rigidity, enhanced proteolytic resistance, and tighter target complementarity compared with the saturated amino acid residues.[2] In particular, inspired by the natural product yaku'amide, bulky tetrasubstituted dhAAs has begun to capture increasing attention as a powerful adamant regulator in peptide modifications.[3] From a retrosynthetic point of view, direct C(sp^2)–H bond functionalization of trisubstituted dhAAs would be an ideal approach to obtain the fully substituted derivatives.[4] However, such a reaction pattern still represents a formidable challenge due to the excessive steric hindrance across the congested C = C double bond. Indeed, previous efforts have mainly focused on the electrophilic halogenation reactions (Scheme 1a), albeit frequently with low stereoselectivity, offering synthetic handles that could be further used in downstream cross-coupling transformations.[5] Alternatively, Maia and Ciufolini independently described the carbon–nitrogen and carbon–carbon bond formation reactions of dhAAs, but still suffering from low *E*/*Z* selectivity or limited substrate scope (Scheme 1b and 1c).[6] In this context, here we report a straightforward and highly stereoselective C(sp^2)–H phosphorylation of trisubstituted dhAAs for the construction of unprecedented fully substituted β-phosphonodehydroamino acids and their application in peptide modifications (Scheme 1d).

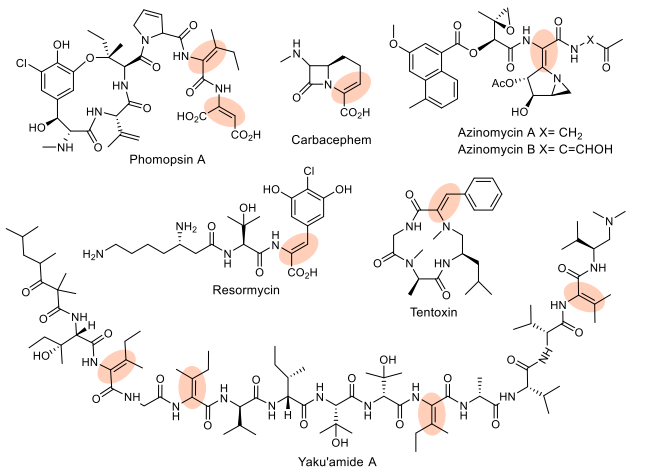

Figure 1. Selected natural products featuring a dehydroamino acid motif.

Phosphono-modified amino acids obtained by replacing the natural O–P bond with an artificial nonhydrolyzable C–P bond could lead to increased resistance to enzymatic degradation, and this strategy has triggered the discovery of numerous amino carboxylic phosphonate mimetics possessing wide applications in medicine and agriculture.[7] With this

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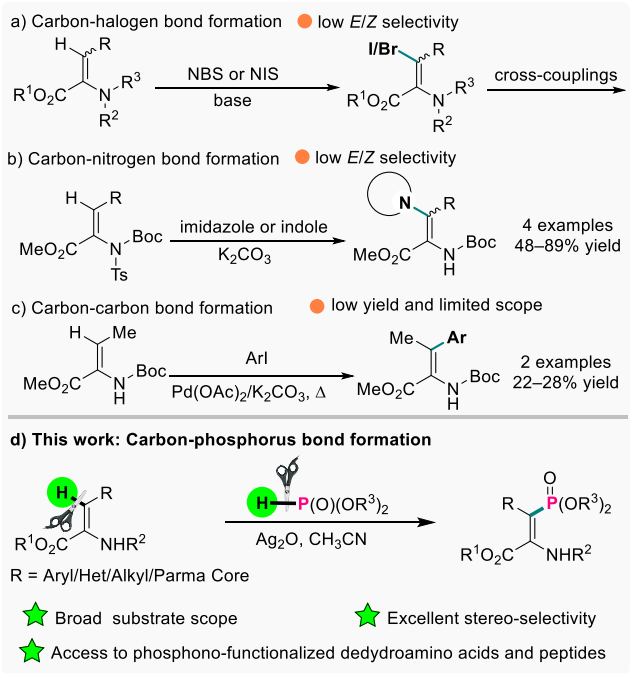
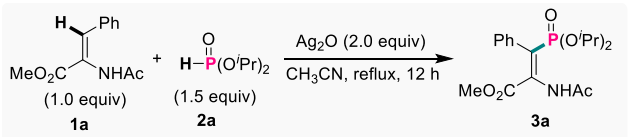
Scheme 1. Bulky C(sp^2)−H Functionalization Reactions of α,β-Dehydroamino Acids



consideration in mind and as a continuing part of our constant interest in phosphonic acid chemistry,[8] we conceived that the cross-dehydrogenative coupling between readily available α,β-dehydro α-amino carboxylic esters and H-phosphites would provide facile access to the valuable β-phosphono dehydroamino acids.[9] In particular, to circumvent the huge steric congestion in the olefin moiety, we turned to a radical relay solution by generating reactive alkyl radical species under silver-promoted conditions which was recently disclosed in our lab for a unique double phosphorylation reaction of enamides.[10] Put it into practice, a series of silver-mediated coupling conditions were investigated between *N*-acetyldehydrophenylalanine **1a** and diisopropyl phosphite **2a** (Figure 2, see the Supporting Information for detailed optimizing results). To our great delight, under the conditions of stoichiometric silver oxide in acetonitrile at reflux, the desired phosphonodehydrophenylalanine **3a** was obtained in up to 75% yield as a single *Z* isomer (X-ray confirmed). Notably, the



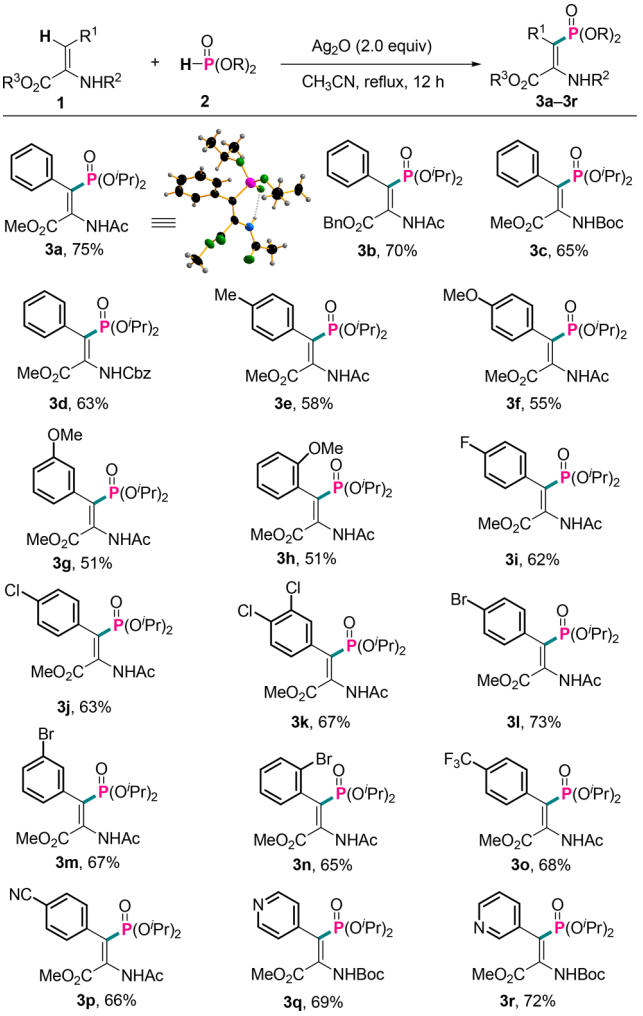
Variation from the standard conditions:	Yield of **3a** / (%)
none	75%, single *Z*-isomer
Ag_2O (1.0 equiv)	31
Ag_2O (0.5 equiv)	7
AgOAc (2.0 equiv)	9
Ag_2CO_3 (2.0 equiv)	5
Cu_2O (2.0 equiv) instead of Ag_2O	0
$Mn(acac)_3$ (2.0 equiv) instead of Ag_2O	trace
DMF instead of CH_3CN	0
40 °C instead of reflux	0

Figure 2. Selected optimizing results

employment of silver oxide proved to be crucial to the occurrence of this transformation, as almost no **3a** was observed when other metal salt was used, such as AgOAc, Ag_2CO_3, Cu_2O, and $Mn(acac)_3$. Reducing the amount of Ag_2O, changing the solvent, or lowering the reaction temperature also severely diminished the yield of **3a**.[11]

The scope of this silver-promoted cross-dehydrogenative coupling reaction was first assessed by the preparation of different β-aryl-substituted phosphono-dhAAs (Scheme 2).

Scheme 2. Scope of β-Aryl- and Heteroaryl-Substituted Phosphonodehydroamino Acids



The change in the carboxylic or amino protecting groups was well compatible (**3b**−**3d**). Electron-donating groups (−Me, −OMe), halogens (−F, −Cl, −Br), and electron-withdrawing groups ($-CF_3$ and −CN) located at various positions on the phenyl ring were all tolerated and gave the corresponding amino carboxylic alkenyl phosphonates **3e**−**3p** in moderate to good yield with constant single *Z*-stereoselectivity. Importantly, both *p*- and *m*-pyridyl-derived dhAA substrates also underwent the highly selective C(sp^2)−H phosphorylation uneventfully, thus affording **3q** and **3r** in 69% and 72% yield, respectively. Subsequently, the application of this protocol to a broad array of β-alkyl-substituted α-dhAAs was operated (Scheme 3). Again, switching the substituents in the amino or carboxylic moiety of **1** and H-phosphites **2** had no significant influence on the reaction outcome (**3s**−**3x**). Substrates **1**

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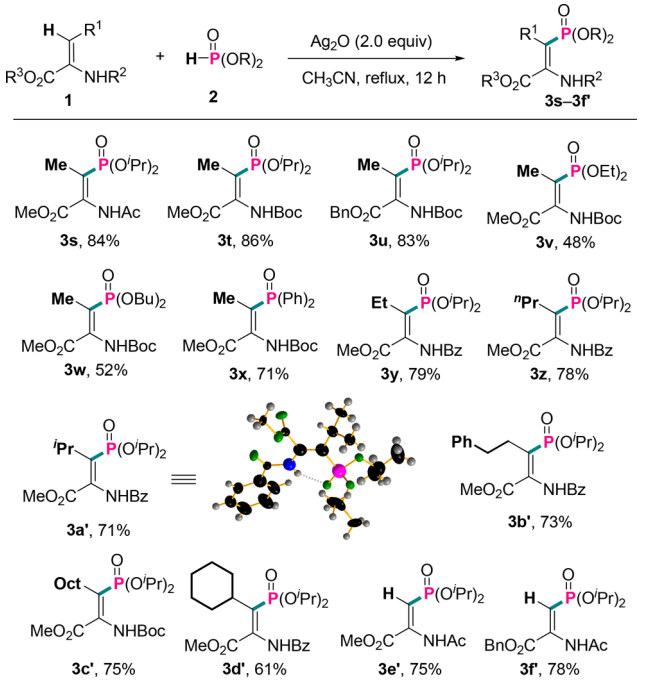
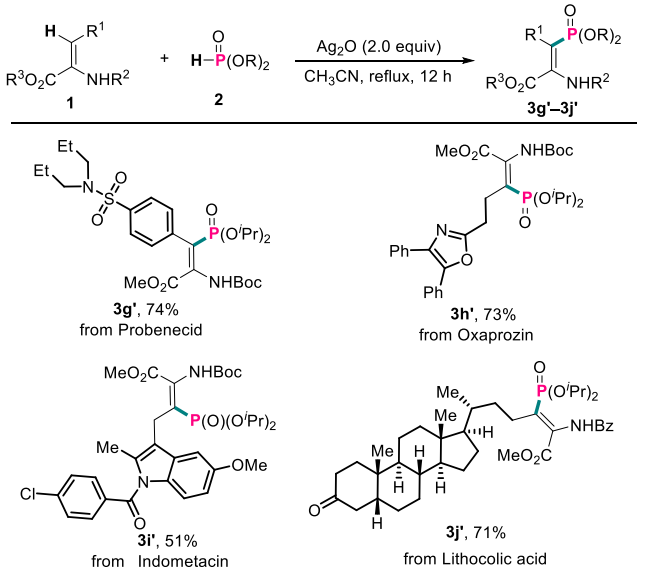
Scheme 3. Scope of β-Alkyl-Substituted Phosphonodehydroamino Acids



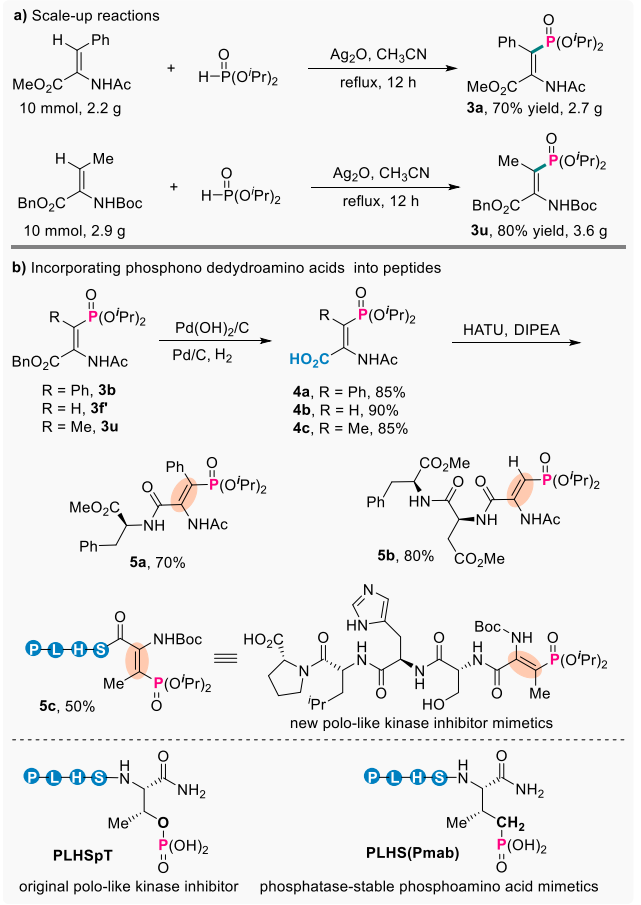
possessing different alkyl groups, including Et, ^{n}Pr, ^{i}Pr, $PhCH_2CH_2$, octyl, and cyclohexyl ones, were easily coupled with **2a** under identical conditions (**3y**–**3d′**). In addition, this reaction is also applicable to disubstituted dhAAs and furnished **3e′** and **3f′** in good yield. More importantly, we were glad to find that trisubstituted α-amino carboxylic alkenes equipped with diverse pharmaceutical cores, including probenecid (**1g′**), oxaprozin (**1h′**), indomethacin (**1i′**), and lithicolic acid (**1j′**), were also tolerated, thus giving rise to the highly functionalized β-phosphono-dhAAs **3g′**–**3j′** as single *Z*-isomers in good yield (Scheme 4).

Scheme 4. Preparation of Pharmacetical Core-Substituted Phosphonodehydroamino Acids



Both β-aryl and β-alkyl dehydroamino acid substrates (**1a** and **1u**) were evaluated on gram scale with almost identical results compared with their model reactions, highlighting the good practicality of this method (Scheme 5a). In these two

Scheme 5. Scale-up Experiments and Synthesis of Phosphono-Functionalized Peptides



cases, the excess Ag_2O and other silver species could be easily recycled, and reused as effective promoter in another round of phosphorylation reaction with similar result, thus significantly improving the economy of this protocol (see the SI for details). The presence of benzyl ester groups in phosphono-dhAAs **3b**, **3u**, and **3f′** could be deprotected easily to liberate the free carboxylic group and thus offered good opportunity for further incorporation into peptide scaffolds (Scheme 5b). Among them, the β-phenyl dehydroamino carboxylic acid **4a** was obtained in 85% yield and connected with phenylalanine to give phosphonodipeptide **5a** in 70% yield. The amino residue of Aspartame was linked with P-hybrid amino acid **4b** to provide the phosphonotripeptide **5b** in 80% yield. Phosphopeptides often have the capacity to act as molecular switches that could regulate protein–protein interactions (PPIs).[12] For example, Lee's group has identified that the minimal phosphopeptides (PLHSpT) could function as selective binding agents targeting the polo-box domain (PBD) of polo-like kinase 1 (PLK1).[13] However, the hydrolytic lability of phosphoryl esters to phosphatases restricted the applicability of such O–P bond-linked phosphopeptides in cellular environments. To overcome this shortage, Burke's group has demonstrated that the binding affinity of PLHS (Pmab) could

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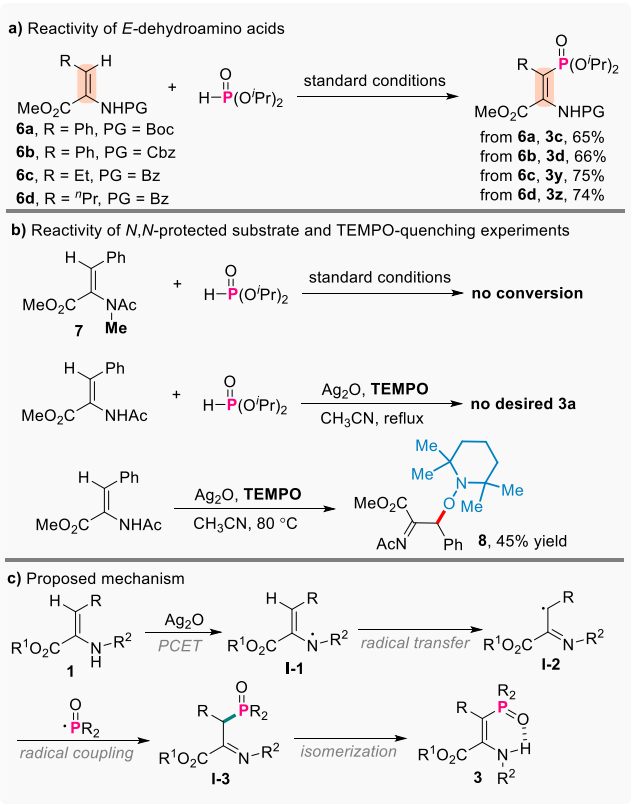
be enhanced several-fold yet retain good selectivity by replacing O−P bond with more stable C−P bond.[14] Inspired by these pioneering studies, we subjected β-methyl dehydroamino acid **4c** to integrate with the Pro-Leu-His-Ser sequence to get the phosphono-pentapeptide **5c** as a new phosphatase-stable analogue of PLHSpT.

All the above-used starting dhAAs feature a *Z*-configuration, and produced the phosphorylation products with absolute *Z*-selectivity. As a comparison, several *E*-dehydroamino carboxylic alkenes (**6a**−**6d**) were also prepared and treated with H-phosphite **2a** under otherwise standard conditions (Scheme 6a). Notably, still only *Z*-phosphono dhAAs (**3c**, **3d**, **3y**, and **3z**) were formed in similar yields as those observed for *Z*-starting materials, suggesting that geometry of the double bond is not a controlling factor in the C−P bond formation step. *N*,*N*-diprotected substrate **7** completely inhibited the transformation, implying that the N−H group may possess a pivotal role in triggering the current reaction. Adding a radical scavenger (TEMPO) to the model reaction system entirely halted the formation of **3a**. Importantly, the alkyl radical-capture product **8** was obtained in 45% yield, thus strongly supporting that an uncommon radical-coupling pathway is presumably operative. Taking these results into consideration,[15] a plausible mechanism was proposed as illustrated in Scheme 6c. First, the N−H bond of trisubstituted dhAAs **1** was activated through a proton-coupled electron transfer (PCET) process initiated by Ag_2O to give *N*-centered radical **I-1**, which isomerized to a more stable alkyl radical **I-2** expeditiously. This radical species was then arrested by a *P*-centered radical to form the imine intermediate **I-3**. Finally, fully substituted alkenyl phosphonate **3** was generated with *Z*-configuration driven by the formation of a hydrogen-bond network in a six-membered ring. The presence of such hydrogen bonds has been unambiguously confirmed in the X-ray structure of compound **3a** and **3a′**.

Scheme 6. Mechanistic Experiments and Proposed Mechanism



In conclusion, a stereoselective C(sp^2)−H phosphorylation reaction of trisubstituted dhAAs was realized by means of a silver-promoted radical relay process. This simple and practical protocol allows us to obtain the bulky tetrasubstituted phosphono-dhAAs on a gram scale along with three new phosphonopeptides. This study not only provides a direct approach for the introduction of valuable phosphonate group into amino acid framework, but also offers new precursors for future asymmetric hydrogenation en route to chiral β-phosphonoamino acids, the research of which is in progress in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02229.

Experimental procedures, characterization data, mechanistic studies, DFT calculations, and NMR spectrum (PDF)

Accession Codes

CCDC 2008589−2008590 and 2008618 contain 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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