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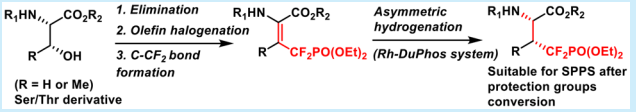
Synthesis of α,α-Difluorinated Phosphonate pSer/pThr Mimetics via Rhodium-Catalyzed Asymmetric Hydrogenation of β-Difluorophosphonomethyl α-(Acylamino)acrylates

Hong-Xue Chen,† Jie Kang,† Rong Chang, Yun-Lai Zhang, Hua-Zhen Duan, Yan-Mei Li, and Yong-Xiang Chen*

Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China

Supporting Information

ABSTRACT: A novel and facile synthetic strategy for α,α-difluorinated phosphonate mimetics of phosphoserine/phosphothreonine utilizing rhodium-catalyzed asymmetric hydrogenation was developed. The dehydrogenated substrate β-difluorophosphonomethyl α-(acylamino)acrylates were first prepared from protected serine/threonine followed by asymmetric hydrogenation using the rhodium−DuPhos catalytic system to generate the chiral center(s). These important phosphonate building blocks were successfully incorporated into phosphatase-resistant peptides, which displayed similar inhibition to the 14-3-3 ζ protein as the parent pSer/pThr peptides.



Serine/threonine phosphorylation is a key protein post-translational modification that regulates diverse cellular signaling pathways.[1] Many cellular protein−protein interactions (PPIs) are mediated by domains that recognize and bind to motifs containing phosphorylated serine or threonine residues.[2] Phosphoproteins and phosphopeptides have provided useful tools for elucidating the biological function of phosphorylation and regulating pSer/pThr involved PPIs.[3] However, the phosphate moiety is hydrolytically labile to phosphatases in a cellular context.[4] To circumvent this limitation, some phosphatase-inert mimetics, in which a nonhydrolyzable methylene (CH_2) or difluoromethylene (CF_2) unit replaces phosphoryl ester oxygen, have been developed for many biological studies and therapeutics designs.[4,5] In comparison with methyl phosphonates, the physicochemical properties of difluoromethyl phosphonates are more similar to those of the corresponding phosphates.[6] However, the syntheses of CF_2-substituted pSer/pThr mimetics, especially in a form suitable for solid-phase peptide synthesis (SPPS) (Figure 1), are still rather challenging.

The construction of a secondary CF_2 phosphonate unit along with two stereocenters largely increases the difficulty of generating a CF_2-substituted pThr mimetic than the pSer one. Dating back to previous pioneering work, there are only a few synthetic strategies available. Berkowitz's group reported that a stereoselective synthesis of CF_2-pThr **2** relied on diastereomerization in a deprotection step[7] (Scheme 1A). Otaka's group described a synthetic approach toward CF_2-pThr **2** utilizing Oppolzer's sultam chiral auxiliary, which first constructed the β-stereocenter utilizing diastereoselective hydrogenation of the olefinic sultam−imide phosphonate derivative followed by stereoselective amination of the α-carbon[8] (Scheme 1A). A more facile synthetic route with higher total yield and fewer steps remains in demand. As for the

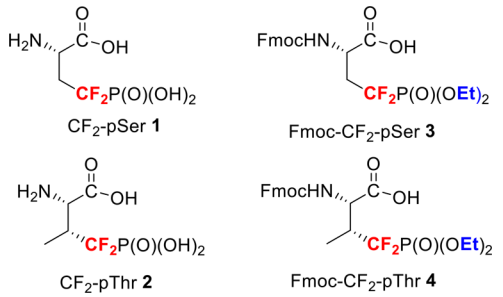


Figure 1. Structures of difluoromethyl phosphonate mimetics of pSer and pThr.

preparation of CF_2-substituted pSer mimetic **1**, among several synthetic approaches[8,9] the recently reported one employed the reaction of a chiral aziridine with the lithium anion of diethyl difluoromethylenephosphonate.[5e,9a] However, the chiral aziridine needs to be prepared either through enzymatic desymmetrization of prochiral *N*-protected serinol or via a five-step synthesis from serine.[10] Thus, it is of great interest to develop a general facile synthetic strategy toward both CF_2-pThr **2** and CF_2-pSer **1**.

In Otaka's route,[8] one of key steps is constructing a β-stereocenter by utilizing diastereoselective hydrogenation of olefinic phosphonate derivative. It inspired us to consider the possibility of simultaneously constructing two stereocenters in CF_2-pThr **2** by employing olefinic asymmetric hydrogenation. Moreover, we noticed that the enantioselective catalyzed hydrogenation of β-alkyl α-(acylamino)acrylates has emerged as a valuable synthetic tool for the preparation of enantiopure

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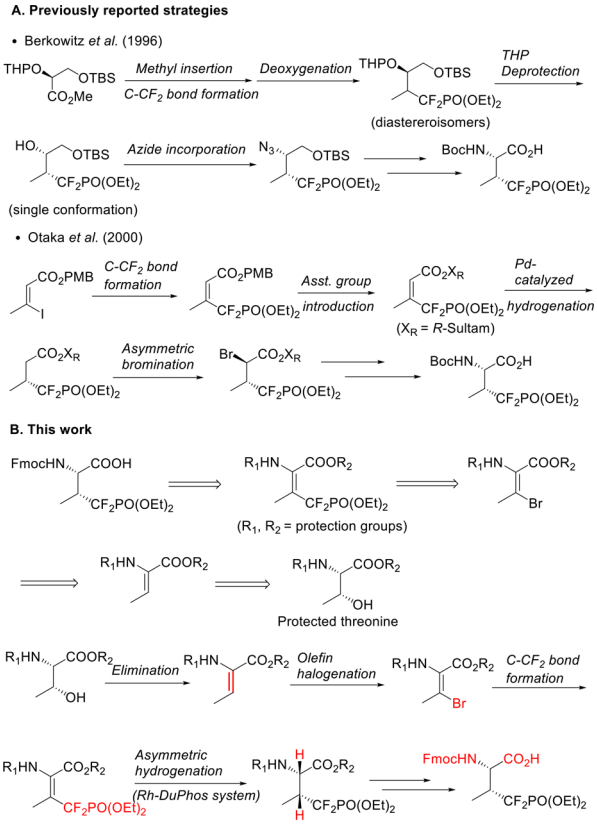
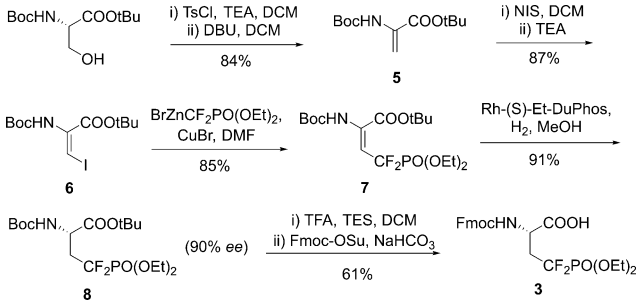
Scheme 1. Previous and Present Synthetic Strategies for CF_2-Substituted pThr Mimetic



α-amino acids derivatives in the past decades.[11] This kind of reaction is usually processed through a rhodium-chelating intermediate involving chiral phosphorus ligand, the C=C double bond, and the acyl C=O group of the substrate.[11a] As a result, the conformation of the α-stereocenter in the product is related to that of the ligand, while the β-stereocenter is determined by the C=C double-bond configuration.[12] Thus, we came up with a new strategy to apply this powerful reaction for the asymmetric synthesis CF_2-pSer **1**/CF_2-pThr **2** and their derivatives. Herein, we report a general synthetic strategy with high total yields to construct *N*-Fmoc-protected CF_2-substituted pSer mimetic **3** and pThr mimetic **4**, which were designed in a form suitable for SPPS, starting from commercially available Ser and Thr derivatives via rhodium-catalyzed asymmetric hydrogenation of β-difluorophosphonomethyl α-(acylamino)acrylates (Scheme 1B).

Following this strategy, we chose commercially available *N*-Boc-protected L-serine α-*tert*-butyl ester as a starting material for the synthesis of *N*-Fmoc-protected CF_2-pSer **3** (Scheme 2). The substrate was first treated with methanesulfonyl chloride and triethylamine to give a sulfonic ester intermediate, followed by β-elimination in the existence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) to yield a dehydroalanine derivative **5**.[13] Next, the β-hydrogen was substituted with an iodo group using *N*-iodosuccinimide (NIS) and triethylamine (TEA) according to previously reported procedures[14] to afford *Z*-form β-iodoacrylate **6**[15] as the predominant product (Z/E = 94:6), whose conformation actually has no effect on the chirality of the final product **3**. The difluoromethylenephosphonate group was introduced to **6** via a Cu(I)-mediated coupling[6b,16] with diethylphosphonodifluoromethyl zinc bromide according to

Scheme 2. Synthesis of *N*-Fmoc-Protected CF_2-pSer 3

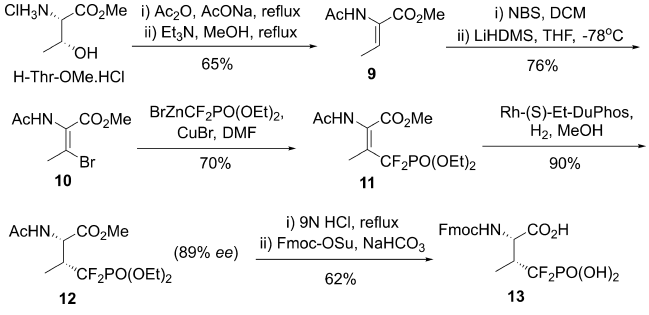


Otaka's procedures.[8] The resultant prochiral substrate **7** was then asymmetrically hydrogenated to construct an α-stereocenter using the Rh–DuPhos system[14] (consisting of the catalyst $Rh(COD)_2BF_4$ and the ligand (*S*,*S*)-Et-DuPhos for enantioselective hydrogenation of α-(acylamino)acrylate to obtain the (*S*)-α-stereocenter[11c]), yielding *S*-form difluoromethyl phosphonate **8** as a predominant product with 90% ee, characterized by chiral HPLC (Supporting Information, SI). The phosphonate **8** was subsequently deprotected by trifluoroacetic acid (TFA) and treated with Fmoc-OSu to give the *N*-Fmoc-protected final product **3**. The total yield of this synthetic route is over 35%, which is a significant improvement compared with previous strategies.[9]

Next, we applied this strategy to the synthesis of *N*-Fmoc-protected CF_2-pThr **4** starting from *N*-Boc-protected L-threonine α-*tert*-butyl ester (Scheme S1). Meanwhile, to ensure that *E*-form prochiral hydrogenation substrate **S3** is the predominant product, the β-halogenation step was slightly modified by a shift to use *N*-bromosuccinimide (NBS) and lithium bis(trimethylsilyl)amide ($LiN(TMS)_2$) instead of NIS and TEA, as previously reported.[17] However, the asymmetric hydrogenation of the tetrasubstituted substrate **S3** was unsuccessful. Over 80% of the substrate was not converted, even after the hydrogen pressure, reaction temperature, and amount of catalysts were increased (Table S1).

It seemed that the addition of the methyl group into the β-carbon of the substrate caused the failure of asymmetric hydrogenation due to steric hindrance. According to some successful attempts of Rh-catalyzed asymmetric hydrogenation of similar tetrasubstituted substrates,[11a,d,14,17a] we estimated that the substitution of the bulky protection groups Boc and *tert*-butyl ester by small protection groups such as acetyl and methyl ester might improve the efficiency of asymmetric hydrogenation. Therefore, L-threonine α-methyl ester hydrochloride was chosen as the starting material instead (Scheme 3). First, it was treated with acetic anhydride and sodium

Scheme 3. Synthesis of *N*-Fmoc-Protected CF_2-pThr 13



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carbonate followed by refluxing to afford *Z*-form *N*-acetyl dehydrobutrate **9**.[18] Then the conversion of **9** to *β*-bromodehydrobutrate **10** employed NBS and $LiN(TMS)_2$ as mentioned above. The subsequent coupling of **10** and difluoromethylenephosphonate was performed according to the same procedure in the synthesis of protected CF_2-pSer **3**. The resultant product, *E*-form prochiral substrate **11** (the conformation was confirmed by NOESY, SI), was then hydrogenated under catalysis of the Rh-(*S*,*S*)-Et-DuPhos system to yield the desired form difluoromethylenephosphonate **12** with 89% ee. As we found that it was unable to remove the *N*-acetyl group and methyl ester group while maintaining the phosphonyl ethyl ester of **12**, the compound was fully deprotected by refluxing in hydrochloride[14] and subsequently treated with Fmoc-OSu to give the final product **13** with a free phosphonate. The overall yield of this synthetic strategy is about 25%, more efficient than previous reactions.[7,8]

To demonstrate the applicability of the obtained *N*-Fmoc-protected CF_2-substituted pSer/pThr mimetics **3**/**13** in Fmoc SPPS, we used them in the synthesis of two phosphopeptide mimetics Pep-CF_2pS **14** and Pep-CF_2pT **15** derived from the substrate sequence of 14-3-3 *ζ* protein (RLYHpSLPA)[19] (Figure 2A). In our previous work,[5a] we incorporated the

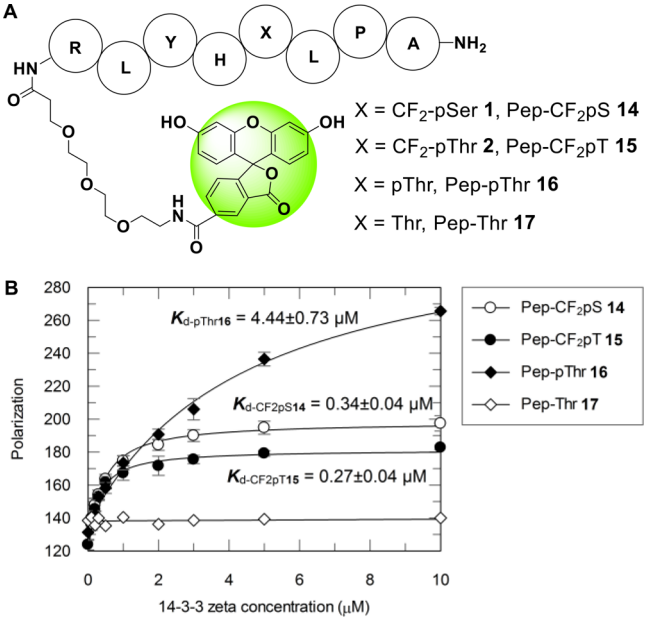

Figure 2. (A) Structures of the synthesized fluorescent peptides. (B) Fluorescence polarization measurements of the fluorescent peptides, respectively. K_d values of all peptides except Pep-Thr **17** were generated by fitting to eq 1 (SI).

CH_2-substituted pSer mimetic into this substrate peptide instead of pSer. The resultant phosphatase-resistant peptide retained 14-3-3 *ζ* binding efficacy similar to the parent pSer-containing peptide. According to the known procedures,[20] we chose rink amide MBHA resin for peptide anchoring to create an amide *C*-terminus, followed by peptide elongation via standard Fmoc SPPS. In order to evaluate the binding affinity of the peptides to 14-3-3 *ζ* by fluorescence polarization, we also introduced 5(6)-carboxyfluorescein (5(6)-FAM) to the *N*-terminus of the peptides. In addition, a triglycerol linker was inserted between the 5(6)-FAM group and the amino acid sequence to minimize the effect of FAM on the protein–peptide interaction. For Pep-CF_2pS **14**, the phosphonyl ethyl ester groups were removed by using a mixture of BSTFA, TBAI, and $BF_3{\cdot}Et_2O$ in DCM prior to peptide detachment from the resin.[8] Finally, the peptides were cleaved from the resin by a mixture of TFA, TIS, and water (95:2.5:2.5 (v)) with all side-chain protection groups removed. After purification by preparative HPLC, the peptides were characterized by analytical HPLC and ESI-MS (SI). In addition, the control peptides Pep-pThr **16** containing natural pThr and non-phosphorylated Pep-Thr **17** (Figure 2A) were prepared following the same synthetic strategy.

Subsequently, we applied fluorescence polarization to measure the binding affinities of these peptides with 14-3-3 *ζ* protein, respectively. Each fluorescent peptide (**14**, **15**, **16**, and **17**) was dissolved and diluted in buffer A (50 mM Tris, 100 mM NaCl, pH = 7.5) to a final concentration of 100 nM and then mixed with an increasing concentration of 14-3-3 *ζ* protein until the polarization value of those peptides reached saturation. The nonphosphorylated Pep-Thr **17** exhibited no obvious change in its polarization value, while all other peptides displayed a sharp increase in polarization signals, indicating the association between those peptides and the protein. These polarization signals were fitted to the saturation titration equation (eq 1, SI)[21] to achieve K_d values. As shown in Figure 2B, Pep-CF_2pS **14** exhibited a K_d value of 0.34 ± 0.04 *μ*M when binding with 14-3-3 *ζ* protein, reflecting a similar affinity to the parent peptide RLYHpSLPA (a K_d value of 0.46 *μ*M[5a]). However, Pep-CF_2pT **15** displayed a K_d value of 0.27 ± 0.04 *μ*M, which indicates a much higher binding affinity with the protein than the naturally phosphorylated Pep-pThr **16** (4.44 ± 0.73 *μ*M). A possible explanation to this difference is that the *β*-methyl group of pThr in Pep-pThr **16** might break some hydrogen bonds nearby between peptide and protein, but the fluorine atoms in Pep-CF_2pT **15** could act as hydrogen bond acceptors, thus recovering some broken hydrogen bonds.

In addition, we have also evaluated the interaction between these peptides and 14-3-3 *ζ* in the presence of alkaline phosphatase (ALP), indicating that phosphonate-containing peptides could be successful replacement of corresponding phosphopeptides as useful tools in cellular context (Figure S4, SI).

In summary, we have developed a novel, practical and efficient strategy to synthesize CF_2-substituted pSer and pThr mimetics via the Rh-DuPhos system catalyzed asymmetric hydrogenation. Before our present work, only the Berkowitz and the Otaka strategies could reach the difluoromethyl phosphonate mimetic of phosphothreonine, while both strategies spend a number of steps in constructing the *α*,*β*-dual-chiral-center structure. Our strategy significantly improves the total yield by constructing two chiral centers in one step through asymmetric hydrogenation of the acrylate substrate, which is achieved using a serial of common reactions under mild conditions starting from commercially available amino acid derivatives. Furthermore, we proved that the Fmoc-protected CF_2-substituted pSer/pThr mimetics can be used in SPPS to generate phosphatase-inert substrate peptides of 14-3-3 *ζ*, which display similar binding efficacy with the parent sequence. Since this strategy could be efficient in large-scale acquisition of the pSer/pThr mimetics, we envisage that it has broad applicability in generating phosphatase-inert phosphopeptides/phosphoproteins used as valuable in vivo tools for probing phosphorylation's role and manipulating pSer/pThr involved PPIs.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and detailed characterization data of all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chen-yx@mail.tsinghua.edu.cn.

ORCID

Yan-Mei Li: 0000-0003-1215-5010

Yong-Xiang Chen: 0000-0003-3518-0139

Author Contributions

†H.-X.C. and J.K. contributed equally.

Notes

The authors declare no competing financial interest.

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