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Palladium-Catalyzed Cross-Coupling of Unactivated Alkylzinc Reagents with 2-Bromo-3,3,3-Trifluoropropene and Its Application in the Synthesis of Fluorinated Amino Acids

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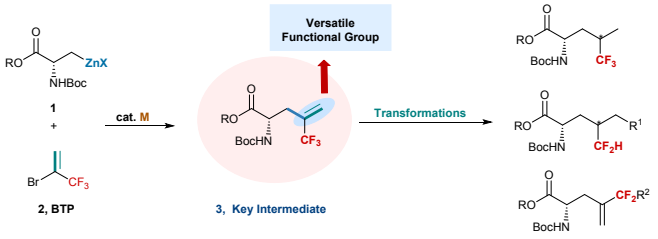
A palladium-catalyzed cross-coupling of unactivated alkylzinc reagents with 2-bromo-3, 3, 3-trifluoropropene (BTP) has been developed, which was used as a key step to prepare a series of trifluoromethylated and difluoromethylated amino acids that are of great interests in peptides/proteins based chemical biology. The advantage of synthesis of these fluorinated amino acids are synthetic simplicity and diversity from a simple and readily available key intermediate α-trifluoromethylalkene-containing amino acid, providing a facile route for applications in medicinal chemistry and life science.

Due to the unique properties of fluorine atom,[1] fluorinated amino acids play a privileged role in discovering new bioactive molecules, peptide engineering and protein structural biology.[2] For examples, fluorinated amino acids have been used as antivirus and antitumor agents,[3] and incorporation of fluorinated amino acids into proteins can enhance their structural stability. Furthermore, peptides or proteins contain such valuable structural motifs can serve as probes for investigation of enzyme kinetics[4] and protein-protein interactions,[5] even as PET-imaging agents.[6] Among the fluorinated amino acids, trifluoromethyl (CF_3) and difluoromethyl (CF_2H) containing amino acids have attracted great attention in peptides/proteins engineering because CF_3 possess high hydrophobicity[7] and CF_2H can serve as a lipophilic hydrogen bond donor[8] , which can enhance the pharmacological properties of peptides and proteins. However, efficient and practical methods to access such valuable fluorinated amino acids are limited.

From the point of view of synthetic simplicity and diversity, we envisioned that the development of an efficient method that can enable access to a key intermediate for the diversity-oriented synthesis would facilitate preparation of diversified trifluoromethylated and difluoromethylated amino acids. 2-Bromo-3,3,3-trifluoropropene (BTP) is a readily available and versatile building block, and has important applications in organic synthesis.[9] The cross-coupling of BTP with protected amino acid zinc reagent would lead to a key fluorinated amino acid for diversity-oriented synthesis by simple transformations of its carbon-carbon double bond (Scheme 1). Herein, we report an efficient and practical strategy to prepare trifluoromethylated and difluoromethylated amino acids with a palladium-catalyzed cross-coupling between unactivated alkylzinc reagent and BTP as a key step. This strategy can enable access to diversified fluorinated amino acids from a key intermediate via simple transformations, thus providing a facile route for applications in peptides/proteins based chemistry.



Scheme 1 Strategy for the diversified synthesis of fluorinated amino acids

According to our hypothesis, initially, we chose an unactivated alkylzinc reagent **4a** as a model substrate to establish a method for construction of the key intermediate **3** (Table 1). To the best of our knowledge, the cross-coupling of unactivated alkylzinc reagents with BTP **2** has not been reported thus far due to the difficulty in suppressing the β-hydride elimination of unactivated alkylzinc reagents. To our delight, an 8% yield of cross-coupling product **5a** was obtained when **4a** was treated with BTP **2** in the presence of $Pd(OAc)_2$ (2.5 mol%) and John-

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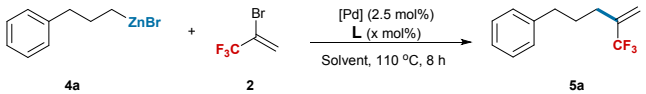
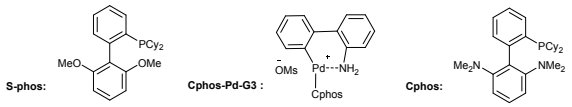
Phos (5 mol%) in THF at 110 °C for 8 h (entry 1). A survey of the phosphine ligands revealed that S-Phos could provide **5a** in 46% yield (entry 5), but other ligands, such as X-Phos, Brett-Phos, and Me-Phos, showed less or no activity (entries 2-4). The choice of solvent is critical to the reaction efficiency. Among the tested solvents (entries 6-9), THF remained the best reaction medium (entry 5). Decreasing the loading amount of S-Phos could improve the yield to 57% (entry 10). Further optimization of the reaction conditions by examining different palladium sources (entries 11-14) showed that palladacyclic complex Cphos-Pd-G3[10] is superior to other tested palladium catalysts (entry 14), providing **5a** in 72% yield, of which the formation of alkene generated by the β-hydride elimination of **4a** was significantly suppressed. The significant reactivity of Cphos-Pd-G3 in the reaction is probablly because an active Pd(0)L species was generated through the reductive elimination of this palladacyclic complex. Decreasing the reaction temperature to 90 °C did not affect the reaction efficiency (entry 15), but 80 °C deminished the yield (entry 16). Notably, the absence of S-Phos still provided **5a** in a comparable yield (71% upon isolation, entry 17), demonstrating that C-Phos is also a suitable ligand in promotion of the reaction.

Table 1 Representative results for optimization of Pd-catalyzed cross-coupling of **4a** with BTP **2**[a]



4a 2 5a

Entry	[Pd]	L (x)	Solvent	Yield(%), **3a**[b]
1	$Pd(OAc)_2$	John-Phos (5)	THF	8
2	$Pd(OAc)_2$	X-Phos (5)	THF	15
3	$Pd(OAc)_2$	Brett-Phos (5)	THF	Trace
4	$Pd(OAc)_2$	Me-Phos (5)	THF	33
5	$Pd(OAc)_2$	S-Phos (5)	THF	46
6	$Pd(OAc)_2$	S-Phos (5)	DMF	5
7	$Pd(OAc)_2$	S-Phos (5)	DCE	13
8	$Pd(OAc)_2$	S-Phos (5)	Dioxane	3
9	$Pd(OAc)_2$	S-Phos (5)	Diglyme	3
10	$Pd(OAc)_2$	S-Phos (2.5)	THF	57
11	$Pd(PPh_3)_4$	S-Phos (2.5)	THF	8
12	$Pd(PPh_3)_2Cl_2$	S-Phos (2.5)	THF	42
13	$Pd(dppf)Cl_2$	S-Phos (2.5)	THF	43
14	Cphos-Pd-G3	S-Phos (2.5)	THF	72
15[c]	Cphos-Pd-G3	S-Phos (2.5)	THF	73 (70)
16[d]	Cphos-Pd-G3	S-Phos (2.5)	THF	43
17[c]	Cphos-Pd-G3	----	THF	72 (71)



[a]Reaction conditions (unless otherwise specified): **4a** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), anhydrous solvent (2.0 mL). [b]Determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard, and the number within parentheses represents the yield of the isolated product. [c]Reaction runs at 90 °C. [d]Reaction runs at 80 °C.

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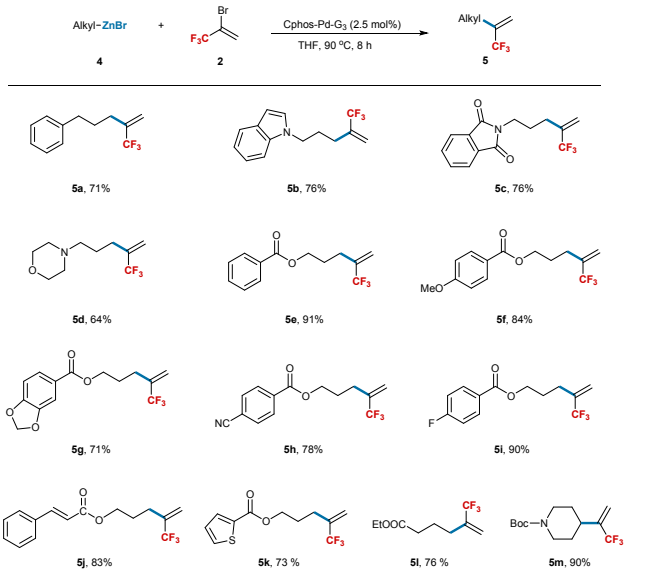
To examine the substrate scope of this palladium-catalyzed process, a variety of unactivated alkylzinc reagents were tested (Table 2). Generally, good to high yields of desired products **5** were obtained. The reaction exhibits good-functional group tolerance. Substrates **4** bearing indole, isoindoline-1,3-dione, morpholine, ester, cyano and fluoride all underwent the cross-coupling smoothly (**5b**-**i**). It should be mentioned that α,β-unsaturated ester (**5j**) and thenyl group (**5k**) containing alkylzinc reagents were also applicable to the reaction, providing the corresponding products with high efficiency. Importantly, the enolizable carboxylic acid ester did not interfere with the reaction (**5l**), thus demonstrating the advantage of current process. Furthermore, the reaction was not restricted to primary alkylzinc reagents, as the secondary alkylzinc reagent was also competent coupling partner as shown in **5m**.

Table 2 Pd-catalyzed cross-coupling of unactivated alkylzinc reagents **4** with BTP **2**[a]



[a]Reaction conditions (unless otherwise specified): **4a** (0.3 mmol, 1.0 equiv), **2** (0.6 mmol, 2.0 equiv), THF (2.0 mL). All reported yields are isolated yields.

With this palladium-catalyzed cross-coupling reaction in hand, we then turned our attention to the synthesis of fluorinated amino acids. Trifluorovaline has important applications in peptide and protein structural biology due to the CF_3 group can enhance the stability of peptides and proteins structure.[11] However, the synthesis of optically pure trifluorovaline usually requires multiple-steps procedure,[12] which restricts its wide-spread synthetic applications. But on the basis of this developed palladium-catalyzed process, optically pure *L*-trifluorovaline can be easily prepared by cross-coupling of BTP with alkylzinc reagent **4n**, followed by hydrogenation. As shown in Scheme 2a, the key intermediate **3** can be obtained on gram-scale with 90% yield, in which $Pd(OAc)_2$/S-Phos instead of Cphos-Pd-G3 was used as a catalyst, thus demonstrating the reliability and practicability of this protocol. Alkene **3** was subsequently reduced by H_2 (6 atm) in the presence of $Pd(OH)_2/C$ to afford a mixture of trifluorovaline diastereoisomers **6**. This mixture can be readily separated by silica gel chromatography. The absolute configuration of (2*S*,4*R*)-trifluorovaline **6a** was assigned by the

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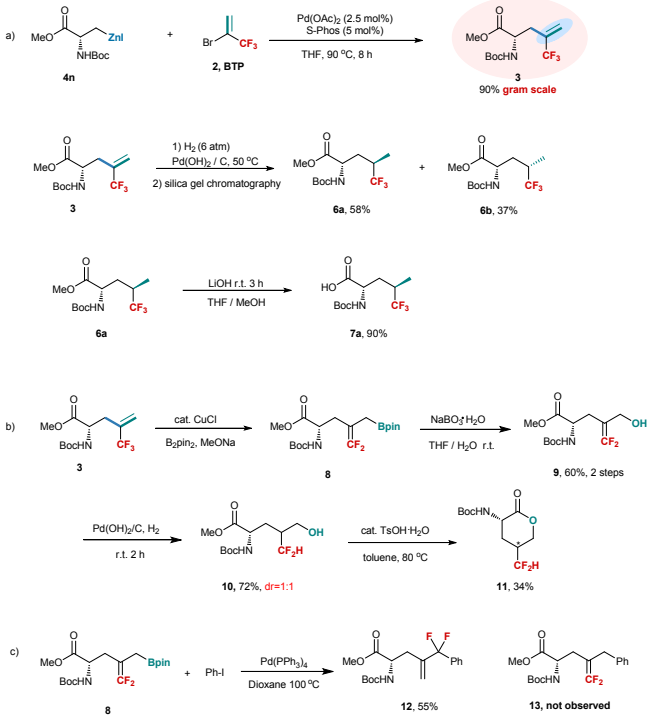
X-ray structure analysis of amino acid **7a**,[13] which was obtained by saponification of **6** with LiOH. Compared to previous reports,[12] the current synthesis of optically pure *L*-trifluorovalines **6a** and **6b** features synthetic simplicity and convenience (2 steps *vs* 5 steps[12b]) without specific procedure, such as enzymatic resolution[12a]. The key intermediate **3** can also be used for the synthesis of difluoromethylated amino acids that otherwise are difficult to prepare by conventional methods. For example, borylation-defluorination of **3** catalyzed by copper[14] afforded *gem*-difluoroalkene containing amino acid **8** efficiently, which can serve as a versatile building block for the further transformations. As shown in scheme 2b, oxidation of C-B bond of **8**,[15] followed by hydrogenation resulted in difluormethylated amino acids **10** efficiently as a mixture of 1:1 diastereoisomers. This diastereoisomeric mixture of amino acids **10** can also be separated by cyclization to form an optical pure six-membered lactone **11**. Furthermore, the borylated amino acid **8** can also be used as a coupling partner for the cross-coupling reaction. Interestingly, the *gem*-difluoroallylic benzene **12** instead of *gem*-difluoroalkene **13** was obtained by treatment of **8** with phenyl iodide via Suzuki reaction (Scheme 2c). This *regio*-selectivity is probably due to the stronger Pd-CF_2R σ-bond as a result of strong electron-withdrawing effect of CF_2 group.[16] Given the fact that the presence of CF_2 at benzylic position can improve the metabolic stability of benzyl-containing amino acids,[17] this transformation may have potential applications in discovering some interesting new bioactive molecules. On the other hand, boronic amino acids have important applications in pharmaceuticals,[18] but efficient methods to access them are limited. This method also provides an efficient route to access this kind of amino acids.



Scheme 2 Synthesis of key intermediate **3** and its applications in diversified synthesis of fluorinated amino acids

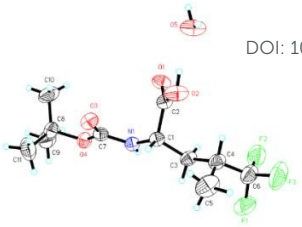


Figure 1 X-ray crystal structure of amino acid **7a**

In conclusion, we have developed a diversity-oriented synthetic strategy to access trifluoromethylated and difluoromethylated amino acids from a simple and versatile intermediate, in which the palladium-catalyzed cross-coupling between unactivated alkylzinc reagents with BTP was established as a key step. The advantage of this strategy is the synthetic simplicity and diversity. All the resulting difluoromethylated and *gem*-difluoroalkene containing amino acids are unknown and can serve as useful building blocks for further transformations or be used for peptides/proteins based chemical biology and drug discovery and development.

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Conflicts of interest

There are no conflicts to declare.

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