Advanced Synthesis & Catalysis

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.202000786

Link to VoR: https://doi.org/10.1002/adsc.202000786

10.1002/adsc.202000786

COMMUNICATION

DOI: 10.1002/adsc.201

Construction of Boronated γ-Lactams via Palladium-Catalyzed Intramolecular Boryldifluoroalkylation of Alkenes

Wu-Jie Lin,[a] Yu-Zhao Wang,[a] Jian-Yu Zou,[a] Yi-Chuan Zhao,[a] Jin-Lin Wang,[a] and Xue-Yuan Liu[a,*]

[a]State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, 730000, People's Republic of China
E-mail: liuxuey@lzu.edu.cn

Received:

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

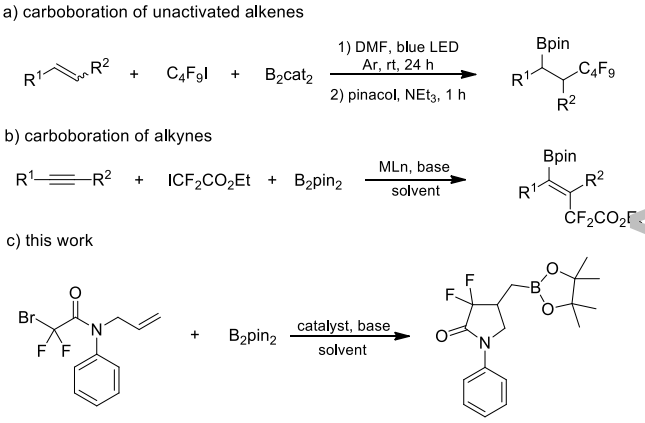
Abstract. An approach for the preparation of boronated γ-lactams via palladium-catalyzed boryldifluoroalkylation of alkenes with α-bromodifluoroacetamides was developed. This method exhibits good functional group tolerance. Various boronated products were obtained in moderate to good yields for 1h. Mechanistic studies indicated that this reaction may involve an intramolecular radical cascade cyclization process.

Keywords: alkenes; boronation; difluoroalkylation; difunctionalization; palladium-catalyzed

Organoboron compounds are useful building blocks in organic synthesis, and the carbon-boron bond can be readily transformed into various functional groups.[1] Considerable efforts have been devoted to the construction of boron-containing molecules.[2] Among various approaches, the difunctionalization of alkenes is one of the most efficient methods,[3] leading to rapidly increase in molecular complexity via a single synthetic operation. In this context, the boryldifluoroalkylation of alkenes has made remarkable achievement owing to the ubiquity of CF_2 group.[4, 5] For examples, in 2018, Studer et al. reported a transition metal-free radical carboboration reaction of unactivated alkenes (Scheme 1a).[5] This method allows the conversion of various unactivated alkenes into 1,2-addition products by light-mediated C-I bond homolysis. Subsequently, Zhu and Zhang reported the novel palladium-catalyzed carboboration reaction of alkynes with fluoroalkyl halides, independently (Scheme 1b).[6] This approach shows high regio- and stereoselectivity and broad substrate scope, *trans*-addition product. However, to the best of our knowledge, intramolecular boryldifluoroalkylation of alkenes is not reported.

Difluoroalkylation reactions have attracted chemists' persistent attention because of the ubiquitous existence of fluorine skeletons in natural products, pharmaceuticals and agrochemicals.[7] Generally, the methods to introduce CF_2 group mainly focus on transition-metal-catalyzed cross-couplings[8] and free radical process.[9] Several elegant examples in transition-metal-catalyzed difluoroalkylation reactions have been developed in recent years, offering efficient routes to construct the fluorinated compounds. For example, Zhang and co-workers developed a palladium-catalyzed Heck-type fluoroalkylation of alkenes with fluoroalkyl halides, which involves a radical pathway. [9i] Our group also reported a palladium-catalyzed regioselective radical difluoroalkylation and carbonylation of alkynes.[10] A visible-light-mediated tandem radical difluoroalkylation of unactivated alkenes was developed by Zhu group.[11] Despite these promising advances,[12] new and efficient methods for incorporating the difluoromethylene group (CF_2) into organic compounds is still highly desirable.

γ-Lactams are common structural motifs found in natural products and pesticides. The CF_2-containing



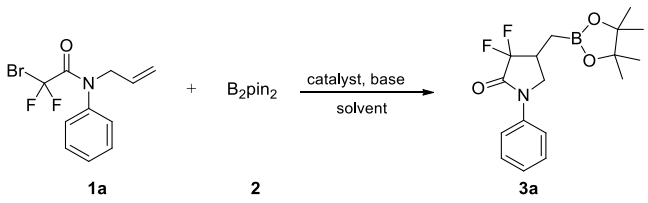
Scheme1. boryldifluoroalkylation of alkenes or alkynes

γ-lactams are of particularly attractive due to their unique pharmacological properties.[13] Consequently, new methods to construct fluorinated γ-lactams are desirable.[14] As part of our ongoing interest in CF_2

chemistry[15] and C-B bond formation, here we report a palladium-catalyzed intramolecular boryldifluoroalkylation of alkenes with B_2pin_2 (Scheme 1c). The reaction involves tandem radical cyclization, and it affords a series of useful 4-boronate ester substituted difluoro-γ-lactams.

Initially, we used *N*-allyl-2-bromo-2,2-difluoro-*N*-phenylacetamide **1a** and B_2pin_2 as model substrates to investigate the feasibility of this reaction (Table 1). When the reaction proceeded with CuI/2, 2'-bpy (10 mol%) and LiO^tBu (1.5 equiv.) in DMF at 60 °C, the desired product **3a** was obtained in 14% yield (entry 1). The use of other representative Cu catalysts, including CuBr and $Cu(CH_3CN)_4PF_6$ did not result in any improvement in yields (entries 1-3). Then we tested commonly used Pd catalysts to improve yields. A 42% yield of **3a** was obtained when $Pd(PPh_3)_4$ was used (entry 4). Then, we continued to examine other reagents to improve yields, the results demonstrated that Cs_2CO_3 was the optimized base (entries 5-9) and obtained the target product in 46% yield. Subsequently, variation of the solvents was then conducted (entries 10-12), which showed acetonitrile (CH_3CN) to be the most efficient (entry 12). When the reaction temperature was raised to 80 °C and the amount of

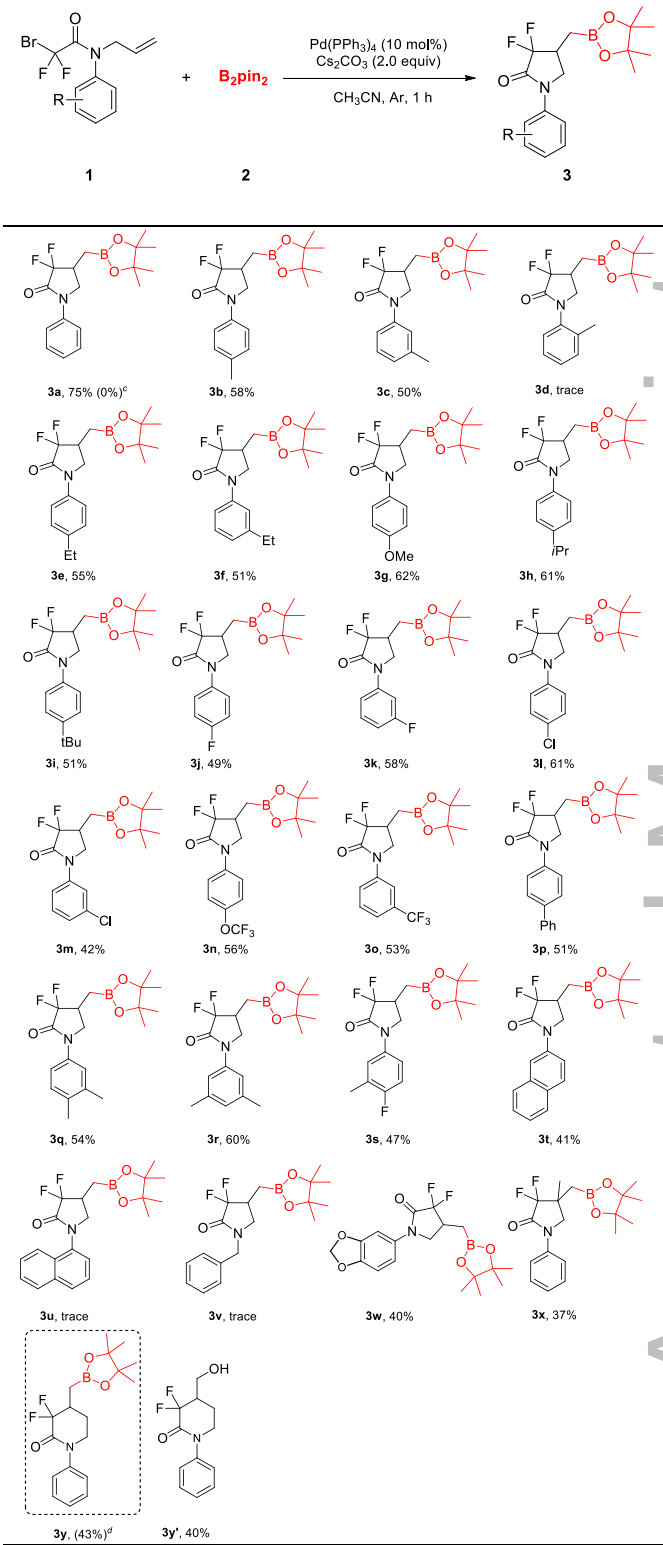
Table 1. Optimization of reaction conditions[a].



Entry	Catalyst/L	Base	Solvent	Yields[b] (%)
1[c]	CuI/2, 2'-bpy	LiO^tBu	DMF	14
2[c]	CuBr/2, 2'-bpy	LiO^tBu	DMF	9
3[c]	$Cu(CH_3CN)_4PF_6$/2, 2'-bpy	LiO^tBu	DMF	13
4[c]	$Pd(PPh_3)_4$	LiO^tBu	DMF	42
5[c]	$Pd(PPh_3)_4$	K_2CO_3	DMF	37
6[c]	$Pd(PPh_3)_4$	Na_2CO_3	DMF	20
7[c]	$Pd(PPh_3)_4$	K_3PO_4	DMF	43
8[c]	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	46
9[c]	$Pd(PPh_3)_4$	Et_3N	DMF	trace
10[c]	$Pd(PPh_3)_4$	Cs_2CO_3	toluene	48
11[c]	$Pd(PPh_3)_4$	Cs_2CO_3	THF	46
12[c]	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	51
13[d, e]	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	65
14[d]	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	72
15[d, f]	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	61
16[d, g]	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	59
17[e]	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	71
18	**$Pd(PPh_3)_4$**	**Cs_2CO_3**	**CH_3CN**	**75**
19	no	Cs_2CO_3	CH_3CN	0
20	$Pd(PPh_3)_4$	no	CH_3CN	0

[a]Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol), catalyst (10 mol%), B_2pin_2 (2.0 equiv) and base (2.0 equiv) in solvent (1.0 mL) at 80 °C under an argon atmosphere for 1 h. [b]Isolated yields. [c]Reaction was performed with base (1.5 equiv), B_2pin_2 (1.5 equiv) at 60 °C for 11 h. [d]B_2pin_2 (1.5 equiv) was used. [e]Reaction was performed for 11 h. [f]Reaction was performed for 2 h. [g]Reaction was performed for 8 h. 2, 2'-bpy = 2, 2'-bipyridine, 1, 10-Phen = 1, 10-phenanthroline.

Scheme 2. Scope of the Bromodifluoroacetamides[a]



[a]Reactions were carried out with **1** (0.1 mmol), B_2pin_2 (2.0 equiv), $Pd(PPh_3)_4$ (10 mol%), and Cs_2CO_3 (2.0 equiv) in CH_3CN (1.0 mL) under Ar atmosphere at 80 °C for 1 h. [b]Isolated yields. [c]Bromodifluoroacetamide was replaced by chlorodifluoroacetamide. [d]NMR yield with methoxybenzine as internal standard.

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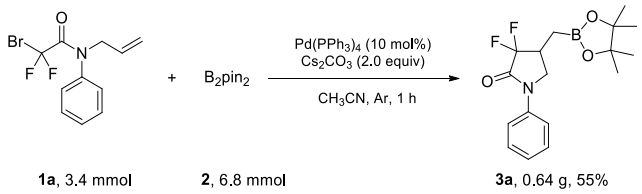
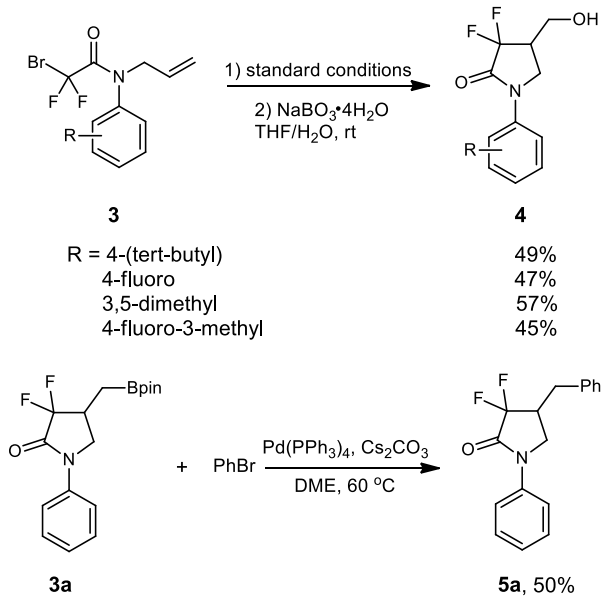
base was increased to 2.0 equivalent, yield gave rise to 65% (entry 13). Notably, shortening reaction time could improve reaction efficiency (entries 14-16). Finally, when the reaction was performed with B_2pin_2 (2.0 equiv) under $Pd(PPh_3)_4$ (10 mol%) as catalyst and Cs_2CO_3 (2.0 equiv) as base at 80 °C for 1 h, resulted in the best result, affording **3a** in 75% yield (entry 18). Control experiments indicated that no desired product was observed in the absence of catalyst or base (entries 19 and 20).

With the optimized reaction conditions established, we studied the substrate scope of this reaction. Various bromodifluoroacetamides were investigated and the results are illustrated in Scheme 2. The bromodifluoroacetamides, bearing electron-donating and electron-withdrawing groups, all worked well in this protocol, affording the corresponding 4-boronated difluoro-γ-lactams in moderate yields (**3b**-**3o**). Substrates with halogen substituents also worked well, offering an entry for further transformation (**3j**-**3m**). Sterically hindered substrates, **1d** and **1u**, failed to produce the desired product. Bromodifluoroacetamide -s with multiple substituents were tolerated, furnishing the desired products in moderate yields (**3q**-**3s**). The substrate bearing heterocyclic substituent was also applicable to this transformation (**3w**). The N-homoallyl amide **1y** also participated in this transformation, generating the 6-exo-trig cyclic product in a moderate yield. The Product **3y** was difficult to separate, so we obtained the corresponding

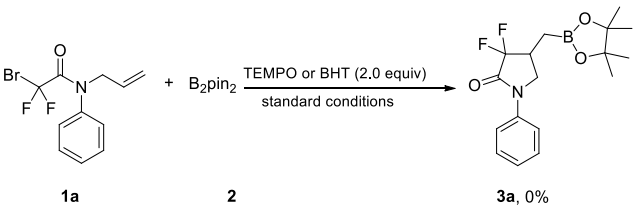
Scheme 3. Scale-up Reaction



Scheme 4. Derivatization of the Product



Scheme 5. Mechanistic Study



hydrolysate **3y'** instead. The structure of **3p** was confirmed by X-ray crystallographic analysis (CCDC No. 2011001).[16]

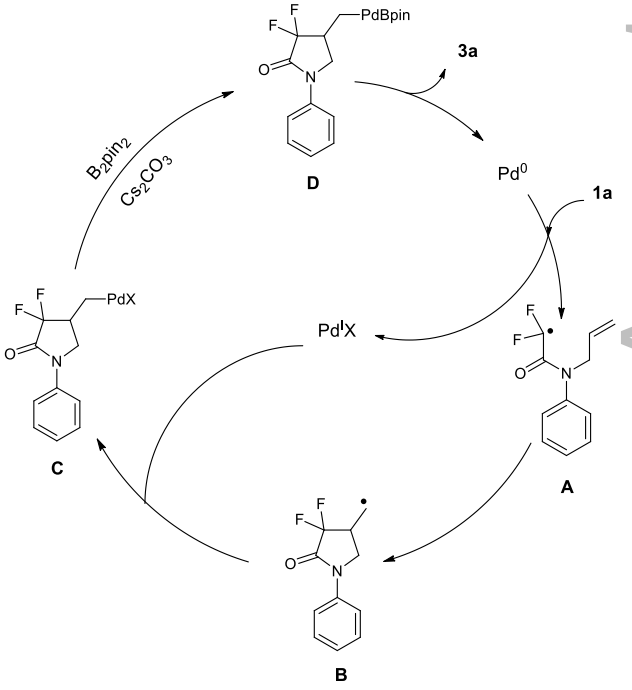
To our delight, this reaction could scaled up to large quantities. When 3.4 mmol of **1a** and 6.8 mmol of **2** were performed under standard conditions, a 55% yield of the desired product **3a** was isolated (Scheme 3).

To showcase the synthetic ultility of this methodology, we studied the derivation of the products (Scheme 4). By treating the product with $NaBO_3 \cdot 4H_2O$, difluoroalkylated alcohols were obtained in moderate yield. Furthermore, by treating **3a** with PhBr in the presence of a palladium catalyst, arylated product **5a** was obtained in 50% yield.

In order to gain the mechanism of this transformation, several control experiments were conducted (Scheme 5). When radical inhibitor (2.0 equiv), TEMPO or BHT, added, the reaction was completely inhibited. These results indicated that a radical pathway might be involved in this process.

On the basis of these experiments and previous reports,[6] a plausible reaction mechanism is shown in Scheme 6. Initially, single electron transfer (SET) between Pd(0) and bromodifluoroacetamide **1a** generates a radical intermediate **A** and Pd(I)X species. Next, an intramolecular cyclization through addition

Scheme 6. Proposed Mechanism



of the fluoroalkyl radical on the double bond affords radical intermediate **B**. Subsequently, the reaction of intermediate **B** with Pd(I)X species forms the Pd(II) intermediate **C**, which undergoes transmetalation with B_2pin_2 to deliver complex **D**. Finally, the reductive elimination of intermediate **D** generates the desired product **3a**. This process also regenerates Pd(0), which enters into the next catalytic circle.

In summary, we have demonstrated a palladium-catalyzed reaction for the construction of 4-boronate ester substituted difluoro-*γ*-lactams. This strategy is easy to operate, and it provides a simple route to produce 4-boronated difluoro-*γ*-lactams that are difficult to access otherwise. The broad substrate scope, short reaction time and potential product derivatization make the boryldifluoroalkylation reactions very attractive. Preliminary mechanistic studies revealed that this reaction may involve an intramolecular difluoroalkyl radical cyclization process. Given that the unique merit of organoboron species, we believe this method has potential application on synthetic chemistry.

Experimental Section

General procedure for the synthesis of 3,3-difluoro-1-phenyl-4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-methyl)pyrrolidin-2-one. To an oven-dried tube was added **1a** (0.1 mmol), B_2pin_2 (0.2 mmol), Cs_2CO_3 (2.0 equiv), and $Pd(PPh_3)_4$ (10 mol%). The tube was evacuated and backfilled with argon (repeated three times). CH_3CN (1.0 mL) was added via syringe. The reaction mixture was stirred at 80 °C for 1 h under Ar atmosphere. After cooling to room temperature, the solvent was evaporated under vacuum. The residue was purified by flash chromatography on silica gel to afford the corresponding product.

Acknowledgements

Financial support from the National Natural Science Foundation of China (21871115) is gratefully acknowledged.

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10.1002/adsc.202000786

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Construction of Boronated γ-Lactams via Palladium-Catalyzed Intramolecular Boryldifluoroalkylation of Alkenes

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Wu-Jie Lin,[a] Yu-Zhao Wang,[a] Jian-Yu Zou,[a] Yi-Chuan Zhao,[a] Jin-Lin Wang,[a] and Xue-Yuan Liu[a,*]