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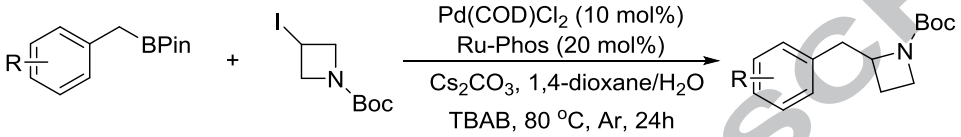

R = Me-, MeO-. i-Pr-, t-Bu-, CF_3O-, F-, Cl-, et.al

Up to 86% yield

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ABSTRACT

An efficient protocol for the synthesis of α-benzyl azetidines starting from benzylboronic acid pinacol ester derivatives and 3-iodoazetidine was developed. A wide range of α-benzyl azetidine derivatives were obtained in moderate to good yields with high regioselectivity (>99%).

Introduction

Saturated nitrogen-containing azetidines have recently received increasing attention due to their unique application values in drug discovery and development.[1] Particularly, 2-benzylazetidines have attracted much attention for its widespread bioactivity[2] and potential pharmaceutical composition.[3] For example, this sort of compounds has a good affinity to TAAR (trace amine-associated receptor) ligands,[4] which are widely used for the treatment of Parkinson's disease and Alzheimer's disease. Several 2-benzylazetidine-containing substances have become the hot spot in drug research for its anticancer activety,[5] anti-inflammatory activety,[6] and anxiolytic property[7] (**Figure 1**).

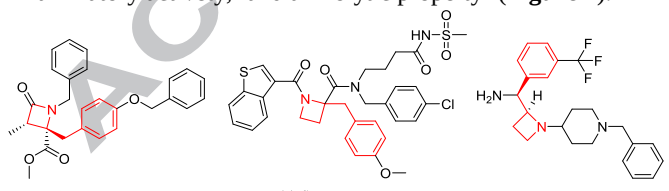

Figure 1. Some pharmaceutical molecules containing 2-benzyl-azetidine scaffolds

Over the past few decades, a variety of protocols for the preparation of azetidines have been reported.[8] In general, azetidines have been obtained by the following methods: a) Intramolecular cyclization of open-chain structures[9] and ~~intermole~~cular cyclization (Scheme 1, a) of primary amines with 1,3-dielectrophiles.[10] b) The ring contraction[11,12]and the ring expansion[2] of saturated nitrogen-containing heterocycles (Scheme 1, b). c) Lithiation-electrophilic substitution of N-thiopivaloylazetidine.[13] Although significant achievements have been made, it is still highly desirable to explore new, mild and straightforward methods for the synthesis of azetidines.

Suzuki reaction is a widely used carbon-carbon bond-forming process, especially in the cross-coupling between alkylboron agents with alkyl halides. Alkyl boron agents such as 9-borabicyclo[3.3.1]nonane(9-BBN borane), alkylboronic acid and potassium trifluoroborate were always utilized in the coupling reaction to construct C(sp^3)-C(sp^3) bonds. 9-BBN borane was used to construct carbon-carbon bonds by Fu's group[14]. In 2002, they reported the similar cross-coupling reaction using alkylboronic acid as nucleophile[15]. In 2012, Molander and coworkers[16] reported the Csp^3-Csp^3 cross-coupling of potassium cyclopropyl-trifluoroborate with benzyl chlorides. In those reactions, the coupling occurred at original position rather than elsewhere. The Pd-catalyzed 1,2-migration in azetidines was less reported. The limited example was established by our group in 2017. In that paper, the first ligand-dependent regio- rearranged and selective Suzuki coupling of 1-Boc-3-iodoazetidine with pyridineboronic acid pinacol ester was reported.[17] However, in the same condition, the cross-coupling reaction of benzylboronic acid pinacol ester with 3-iodoazetidine cannot be achieved. As part of our particular interest in the development of novel

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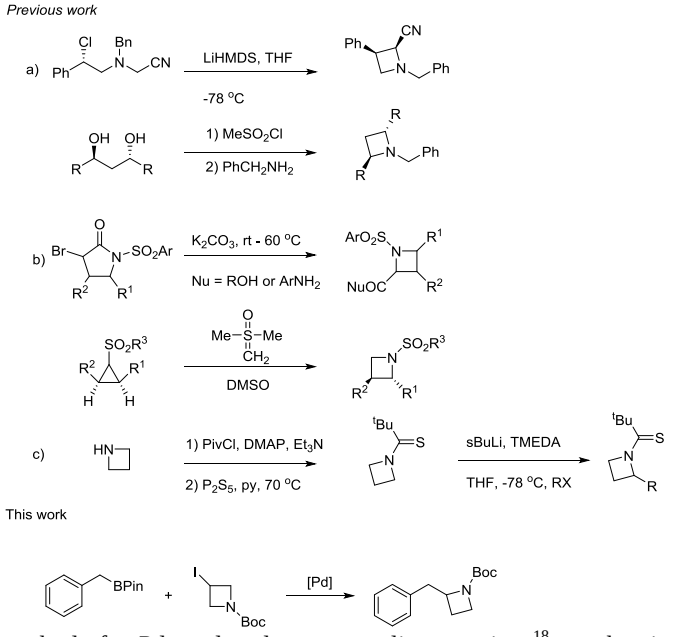
Scheme 1. Typical methods for the synthesis of 2-substituted azetidines.



methods for Pd-catalyzed cross-coupling reactions[18], we herein report an efficient Pd-catalyzed Suzuki coupling of benzylboronic acid pinacol ester derivatives with 3-iodoazetidine to construct α-benzyl azetidines.

Results and Discussion

In order to optimize the reaction conditions, the Suzuki-coupling of 3-iodoazetidine with benzylboronic acid pinacol ester was chosen as model reaction (**Table 1**). Initially, the conditions of arylation of azetidines reported earlier were used in this reaction, but no desired product was obtained. Then $Pd(PPh_3)_4$ which usually used in Suzuki reactions was tested, and the desired α-substituted product **2a** was obtained in 31% yield along with 14% of **3a** (see supporting information (SI)). Then, other palladium sources were screened and the results were summarized in **Table 1**. All catalysts generated from XPhos provided the α-substituted product (**2a**) rather than the β-substituted one with good regioselectivity (>99%) indicated that the choice of ligand might influence the regioselectivity of products (**Table 1**, entries 1-5). Various palladium precursors ($Pd_2(dba)_3$, $Pd(acac)_2$, $PdCl_2(NBD)$, $Pd(COD)Cl_2$ and $Pd(OAc)_2$) were investigated (**Table 1**, entries 1-5), and $Pd(COD)Cl_2$ was found to give a better result with 40% yield. Increasing the amount of substrate **1a** led to an improvement in the yield (see supporting information). Using 2.0 equiv of **1a** gave a good yield of the desired product. Then a series of bases such as K_3PO_4, Na_2CO_3, Cs_2CO_3, CsF, and NaOH were studied, and $Cs_2CO_3$was proved to be the optimal one to afford the α-substituted product in moderate yield with good regioselectivity (**Table 1**, entries 6-10). Then, the mixed solvents were screened (solvent: water = 1:1, v/v) (**Table 1**, entries 11-15). The results indicated that polar aprotic solvents, such as DMSO, DMF and NMP were less effective for the reaction (**Table 1**, entries 11-13), and 1,4-dioxane was the best one compared with DME and THF (**Table 1**, entries 10 vs 14, 15). Furthermore, a variety of ligands such as PPh_3, dppf, dppp, Xant-Phos, DavePhos, CyJhonPhos, Ru-Phos and S-Phos were also examined. The electron-rich monophosphine ligands were found to provide the desired product in higher yields. Whereas, electron-deficient one resulted in lower yield (**Table 1**, entries 16-19 vs 20). Diphosphine ligands were not good for the reaction (**Table 1**, entries 21-23). RuPhos afforded a better yield for the α-substituted product (67%) than XPhos (62%) (**Table 1**, entries 19 vs 10). When sterically hindered monophosphine ligand was used, the reaction yield improved significantly and the target product was obtained in high regioselectivity. Finally, additives such as LiCl, TBAB, $CuBr_2$ were further screened, and TBAB was found to be the optimal one (**Table 1**, entries 24-26). Thus, the optimum reaction conditions were obtained: benzylboronic acid pinacol ester **1a** (1.0 mmol), 1-Boc-3-iodoazetidine **4a** (0.5mmol), $Pd(COD)Cl_2$ (0.05 mmol), RuPhos (0.10 mmol), TBAB (0.05 mmol) and Cs_2CO_3 (1.5 mmol) in 3 mL 1,4-dioxane/H_2O (1:1) at 80 °C under argon atmosphere for 24 h. The structure of product **2a** was confirmed by X-ray crystallographic analysis (**Figure 2**) [19].

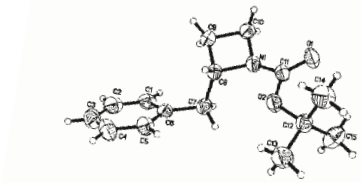
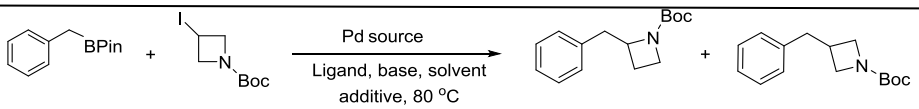


Figure 2. X-ray structure of **2a**

Table 1. Reaction Conditions Optimization[a]



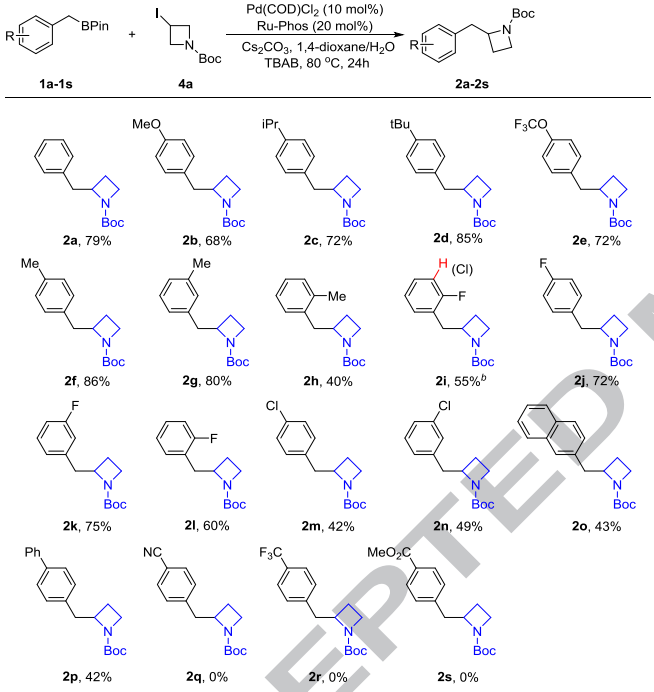
1a 4a 2a 3a

entry	catalyst	base	solvent(ratio=1:1)	ligand	additive	yield of 2a(%)[b]
1	$Pd_2(dba)_3$	Na_2CO_3	dioxane/H_2O	X-Phos	-	17[c]
2	$Pd(acac)_2$	Na_2CO_3	dioxane/H_2O	X-Phos	-	6[c]
3	$PdCl_2(NBD)$	Na_2CO_3	dioxane/H_2O	X-Phos	-	37[c]
4	$Pd(COD)Cl_2$	Na_2CO_3	dioxane/H_2O	X-Phos	-	40[c]
5	$Pd(OAc)_2$	Na_2CO_3	dioxane/H_2O	X-Phos	-	10[c]
6	$Pd(COD)Cl_2$	CsF	dioxane/H_2O	X-Phos	-	0
7	$Pd(COD)Cl_2$	K_3PO_4	dioxane/H_2O	X-Phos	-	46
8	$Pd(COD)Cl_2$	Na_2CO_3	dioxane/H_2O	X-Phos	-	50
9	$Pd(COD)Cl_2$	NaOH	dioxane/H_2O	X-Phos	-	39
10	$Pd(COD)Cl_2$	Cs_2CO_3	dioxane/H_2O	X-Phos	-	62
11	$Pd(COD)Cl_2$	Cs_2CO_3	DMSO/H_2O	X-Phos	-	14
12	$Pd(COD)Cl_2$	Cs_2CO_3	DMF/H_2O	X-Phos	-	6
13	$Pd(COD)Cl_2$	Cs_2CO_3	NMP/H_2O	X-Phos	-	10
14	$Pd(COD)Cl_2$	Cs_2CO_3	THF/H_2O	X-Phos	-	24

15	$Pd(COD)Cl_2$	Cs_2CO_3	DME/H_2O	X-Phos	-	34
16	$Pd(COD)Cl_2$	Cs_2CO_3	dioxane/H_2O	DavePhos	-	35
17	$Pd(COD)Cl_2$	Cs_2CO_3	dioxane/H_2O	CyJohnPhos	-	26
18	$Pd(COD)Cl_2$	Cs_2CO_3	dioxane/H_2O	S-Phos		30
19	$Pd(COD)Cl_2$	Cs_2CO_3	dioxane/H_2O	Ru-Phos	-	67
20	$Pd(COD)Cl_2$	Cs_2CO_3	dioxane/H_2O	PPh_3	-	4
21	$Pd(COD)Cl_2$	Cs_2CO_3	dioxane/H_2O	Dppf	-	10
22	$Pd(COD)Cl_2$	Cs_2CO_3	dioxane/H_2O	Dppp	-	0
23	$Pd(COD)Cl_2$	Cs_2CO_3	dioxane/H_2O	Xant-Phos	-	0
24	$Pd(COD)Cl_2$	Cs_2CO_3	dioxane/H_2O	Ru-Phos	LiCl	77
25	$Pd(COD)Cl_2$	Cs_2CO_3	dioxane/H_2O	Ru-Phos	TBAB	84(79%[d])
26	$Pd(COD)Cl_2$	Cs_2CO_3	dioxane/H_2O	Ru-Phos	$CuBr_2$	78

[a]Reactions conditions: **1a** (1.0 mmol), **4a** (0.5 mmol), $Pd(COD)Cl_2$(0.05 mmol), ligand (0.10 mmol), base (1.5 mmol), additive (0.05 mmol), in solvent (3 mL, organic solvent : H_2O = 1 : 1) at 80 °C for 24 h unless otherwise noted. [b]Determined by GC-MS using n-dodecane as an internal standard. [c]Ratio of **1a** : **4a** = 1.2 : 1, **1a** (0.6 mmol). [d]Isolated yield. TBAB = tetra-n-butylammoniumbromide, NBD = 2,5-norbornadiene, COD = 1,5-cyclooctadiene.

Scheme 2. Synthesis of α-benzyl azetidine derivatives[a]

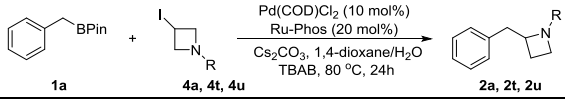


[a]Reactions conditions: benzylboronic acid pinacol ester (1.0 mmol), N-Boc-3-iodoazetidine (0.5mmol), dichloro(1,5-cyclooctadiene)palladium(II) (0.05 mmol), Ru-Phos (0.1 mmol), TBAB (0.05 mmol) and Cs_2CO_3 (3.0 mmol) in solvent (3 mL, organic solvent : H_2O = 1 : 1) at 80 °C for 24 h unless otherwise noted. Isolated yields. The possible α/β isomers were estimated to be >99% compared with the desired products. [b] Product **2i** was obtained from the substrate2-(3-chloro-2-fluorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **1i**.

Under the optimal reaction conditions, various benzylboronic acid pinacol esters **1a-1s** were reacted with 3-iodoazetidine (**4a**) to give desired α-benzyl azetidine derivatives **2a-2s** in moderate to good yields with excellent regioselectivities (>99%). The benzylboronic acid pinacol esters possessing electron donating group (MeO (**1b**), *i*-Pr (**1c**), *t*-Bu (**1d**) and Me (**1f**) on the para-position worked efficiently. The substrate with methyl group on the *meta*-position gave the similar performance to that on *para*-position (**2f**, **2g**). When benzylboronic acid pinacol esters **1h** bearing a methyl group on *ortho*-position was used, the desired **2h** was obtained in low yield which might due to the steric hindrance. The trifluoromethoxy bearing substrate gave the desired product in 72% yield (**2e**). When 2-, 3-, and 4-fluorobenzylboronic acid pinacol ester were used in the reaction, the desired products were obtained in 60%, 75%, and 72%, respectively. In case of *meta*-, and *para*-chlorobenzylboronic acid pinacol ester, the moderate yields of the desired products were obtained (**2m**, **2n**). However, 2-(3-chloro-2-fluorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane gave the dechlorination product **2i** in the same conditions. Notably, when the phenyl ring of benzylboronic acid pinacol ester was replaced by naphthyl or biphenyl group, the target product was obtained in 43%, 42% yields, respectively (**2o, 2p**). Unfortunately, the substrates containing electron-withdrawing groups were not suitable for this system (**2q, 2r** and **2s**).

Different protecting groups on the nitrogen-atoms of 3-idoazetidines were also examined (**Scheme 3**). Substrate bearing -Cbz protecting group could afford the desired product in good yields (entry 2). Whereas, the one with -Ts group didn't compatible in this reaction.

Scheme 3. Synthesis of α-benzyl azetidine derivatives with other protecting groups[a]



entry	R	product	yield
1	Boc (4a)	2a	84%
2	Cbz (4t)	2t	86%
3	Ts (4u)	2u	trace

[a]Reactions conditions: **1a** (1.0 mmol), 3-iodoazetidine (0.5 mmol), $Pd(COD)Cl_2$ (0.05 mmol), Ru-Phos (0.1 mmol), TBAB (0.05 mmol) and Cs_2CO_3 (3.0 mmol) in solvent (3 mL, organic solvent : H_2O = 1 : 1) at 80 °C for 24 h unless otherwise noted. Isolated yields. The possible α/β isomers were estimated to be >99% compared with the desired products (See Supporting Information for details).

Conclusions

In conclusion, a convenient, efficient and practical palladium-catalyzed regioselective protocol for the $C(sp^3)$-$C(sp^3)$ bond formation through the reaction of benzylboronic acid pinacol esters and 3-iodoazetidine was developed. The method shows good functional group tolerance and affords a variety of α-benzyl azetidine derivatives in moderate to good yields with high regioselectivity (>99%). In addition, this method provides an operationally simple and mild strategy for the preparation of α-benzyl azetidines which will be valuable building blocks in material science and drug discovery.

Acknowledgments

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19 Crystallographic data for the structure has been deposited with the Cambridge Crystallographic Data Centre (CCDC 1876328).

Highlights

- A new approach to construct C(sp3)-C(sp3) bond was developed.
- α-benzyl azetidine derivatives were obtained with high regioselectivity (>99%).
- This catalytic system features mild conditions and good substrate tolerance.