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Palladium-Catalyzed Cross-Coupling of Stereospecific Potassium Cyclopropyl Trifluoroborates with Aryl Bromides

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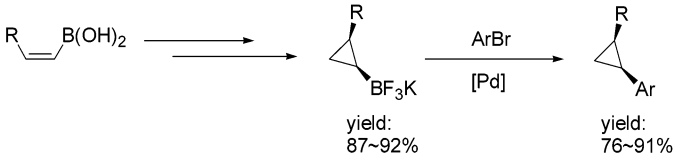
ABSTRACT



Stereospecific cyclopropanation of alkenylboronic esters of pinacol followed by in situ treatment with excess KHF_2 afforded the corresponding potassium cyclopropyl trifluoroborates in high yields, which then underwent Suzuki–Miyaura cross-coupling reactions with aryl bromides to give cyclopropyl-substituted arenes in good yields with retention of configuration. This promises to be a useful method for the synthesis of enantiomerically pure cyclopropanes.

A growing number of cyclopropyl-containing natural products have been isolated and synthesized.[1] Cyclopropanes are also increasingly incorporated into pharmaceuticals due to their well-defined three-dimensional structure.[2] Therefore, the stereocontrolled synthesis of cyclopropane derivatives has attracted considerable interest in recent years.

Alkenylmetal compounds (B, Al, Si, Sn) are versatile intermediates because after cyclopropanation they can potentially react with a variety of electrophiles.

Among the powerful palladium-catalyzed cross-coupling of electrophiles with organometallic reagents, the Suzuki−Miyaura cross-coupling reaction of organoboron compounds has especially attracted chemists' attention.[3] The organoboron reagents are less toxic and more easily accessed by a variety of routes. The conditions are mild, and the reaction is highly selective and tolerant of a broad range of functional groups. In the studies on Suzuki−Miyaura coupling reactions, various organoboranes,[4] boronic acids,[5] and boronic esters[6] were most often employed. Although boronic acids and esters have often been widely utilized in cross-coupling reaction, much attention has been focused on the preparation of various organoboron derivatives. Compared with commonly used organoboron compounds, organotrifluoroborates have distinguishing features: greater nucleophilicity, ready accessibility, and re-

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markable stability in air. Palladium-catalyzed cross-coupling reactions of potassium organotrifluoroborates have been reported by Genet, Molander, and others.[7]

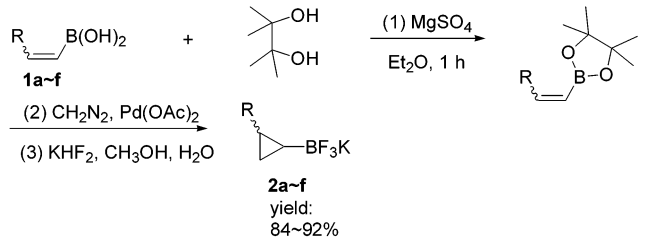
It was well-known that boronic esters allow for the introduction of chiral auxiliaries, thus enabling diastereoselective cyclopropanations of alkenylboronic esters.[8] Furthermore, the alkenylboronic esters are conveniently cyclopropanated by the Pd-catalyzed decomposition of diazomethane to furnish cyclopropylboronic esters. But there were few reports concerning the preparation of stereospecifically chiral *cis*-cyclopropanes.

In our previous work, we have reported that *trans*-alkenylboronic acids could be condensed with chiral diols under reflux for a long period of time,[8c] but it was found that these conditions caused the isomerization of *cis*-alkenylboronic acid. Pietruszka's chiral diol could be condensed with alkenylboronic acids smoothly under mild conditions,[9] but cyclopropylboronic esters of chiral diols are reluctant to take part in cross-coupling reactions[8d,10] and are difficult to hydrolyze,[11] so it was necessary to first reduce using an excess of $LiAlH_4$ and then hydrolyze to obtain cyclopropylboronic acids before further transformation was possible.

With our ongoing interest in the synthesis of enantiomerically pure cyclopropanes, we attempted to find a new way to obtain enantiomerically pure cyclopropanes including the cis isomers. Recently, we studied the stereodefined preparation of racemic potassium cyclopropyl trifluoroborates generated from cyclopropylboronic esters of pinacol and their cross-coupling reactions with aryl bromides as an array of model experiments, because pinacol can also be condensed with boronic acids smoothly. Herein we report our preliminary results.

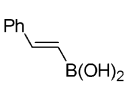
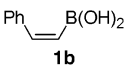
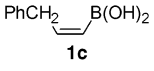
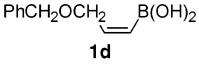
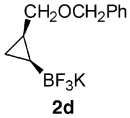
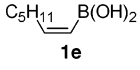
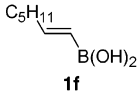
Alkenylboronic acids 1 were easily condensed with pinacol at room temperature to give the corresponding esters in quantitative yield. Cyclopropanation of the esters via palladium-catalyzed decomposition of CH_2N_2[12] followed by in situ treatment with excess KHF_2[7a,13] afforded the stereodefined potassium cyclopropyl trifluoroborates in good to excellent yield (Scheme 1).

Scheme 1



The results obtained are shown in Table 1. As evidenced by 2D NOESY spectra, the cyclopropyl trifluoroborates generated from (*E*)-alkenylboronic acids have trans configurations, while the ones obtained from (*Z*)-alkenylboronic

Table 1. Stereospecific Preparation of Potassium Cyclopropyl Trifluoroborates[a]

entry	alkenylboronic acids **1**	products **2**	yield[b] (%)
1	 **1a**	 **2a**	92
2	 **1b**	 **2b**	90
3	 **1c**	 **2c**	85
4	 **1d**	 **2d**	84
5	 **1e**	 **2e**	88
6	 **1f**	 **2f**	87

[a] (1) The mixture of alkenylboronic acid (10 mmol), pinacol (10.5 mmol), 20 mL of Et_2O, and 0.6 g of $MgSO_4$ was stirred for 1 h at room temperature. (2) To the mixture of alkenylboronic esters (10 mmol), $Pd(OAc)_2$ (122 mg) in 50 mL of Et_2O, was added a 2 M solution of CH_2N_2 in 100 mL of Et_2O at 0 °C for 1 h and then for additional 1 h at room temperature. (3) The mixture of KHF_2 (70 mmol), cyclopropylboronic esters, 35 mL of methanol, and 7 mL of water was stirred for 4 h at room temperature. [b] Isolated yields based on alkenylboronic acids used.

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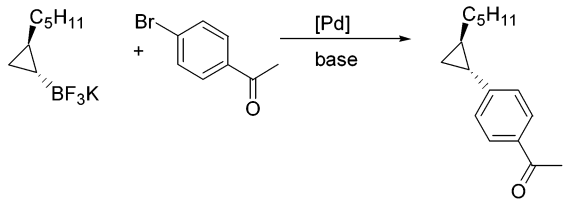
acids have cis configurations. The model experiments may open the door to prepare various chiral potassium cyclopropyl trifluoroborates involving chiral *cis*-cyclopropyl trifluoroborates in particular from the corresponding alkenylboronic ester of the chiral diols.

With various potassium cyclopropyl trifluoroborates **2** in hand, we then investigated Suzuki−Miyaura cross-coupling reactions of **2** with aryl bromides. The conditions for carrying out the Suzuki−Miyaura coupling reaction were optimized by using potassium *trans*-2-pentylcyclopropyl-trifluoroborate **(2f)** and 4-bromoacetophenone as the substrates. The results are indicated in Table 2.

Table 2. Effects of Ligands and Solvents on the Coupling Reaction of Potassium *trans*-2-Pentylcyclopropyl Trifluoroborates with 4-Bromoacetophenone[a]



entry	coupling conditions	yield[b] (%)
1	$PdCl_2$(dppf), *t*-$BuNH_2$, H_2O, *i*-PrOH	NR
2	$PdCl_2$(dppf), Et_3N, *n*-PrOH	NR
3	$PdCl_2$(dppf), Cs_2CO_3, THF, H_2O	91
4	$PdCl_2$(dppf), K_3PO_4·$3H_2O$, toluene, H_2O	86
5	$Pd(OAc)_2$, ligand,[c] K_3PO_4·$3H_2O$, toluene, H_2O	89
6	$Pd(PPh_3)_4$, K_3PO_4·$3H_2O$, toluene, H_2O	87

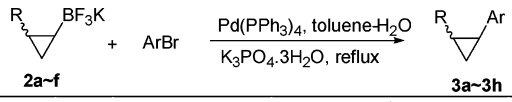
[a] The mixture of potassium *trans*-2-pentylcyclopropyl trifluoro borates (1.2 mmol), 4-bromoacetophenone (1 mmol), 2 mol % of catalyst, 3 mmol of base in various organic solvents (3 mL), and water (1 mL) was refluxed for 20 h under N_2 atmosphere. [b] Isolated yields based on 4-bromoacetophenone. [c] Ligand is 4 mol % of 2-biphenyldicyclohexylphosphine.

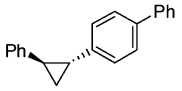
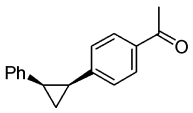
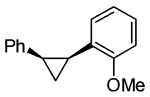
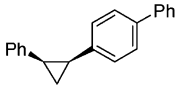
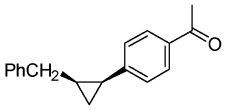
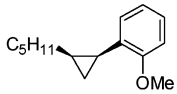
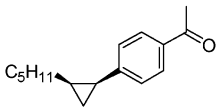
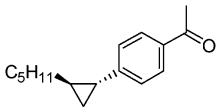
Molander reported that with *i*-PrOH−H_2O as cosolvents and *t*-$BuNH_2$ or NEt_3 as base, the palladium-catalyzed cross-coupling reactions of potassium alkenyltrifluoro-borates with aryl bromides can proceed smoothly.[7b] However, the conditions mentioned above were not effective in our case (Table 2, entries 1 and 2). Using another method[7b] developed by Molander, which was slightly modified by us (decreasing the amount of palladium catalyst), we obtained the desired cross-coupling product in high yield (Table 2, entry 3). To avoid employing expensive Cs_2CO_3, we reinvestigated the coupling conditions and found that using cheaper K_3PO_4·$3H_2O$ as base instead of Cs_2CO_3 and toluene in place of THF, we also obtained the desired coupling products in satisfactory yield (Table 2, entry 4). Further studies illustrated that the combination of $Pd(OAc)_2$ and 2-biphenyldicyclohexylphosphine or $Pd(PPh_3)_4$ rather than $PdCl_2$(dppf) as catalyst also furnished the products **(3h)** in satisfactory yields (Table 2, entries 5 and 6).

The conditions (Table 2, entry 6) were subsequently applied to study the cross-coupling reaction of various stereodefined potassium cyclopropyl trifluoroborates with aryl bromides, considering $Pd(PPh_3)_4$ and K_3PO_4·$3H_2O$ are easily obtained and cheap. The results are summarized in Table 3.

As outlined in Table 3, both *cis*- and *trans*-cyclopropyl trifluoroborates readily reacted not only with the aryl

Table 3. Cross-Coupling Reaction of Potassium Cyclopropyl Trifluoroborates with Aryl Bromides[a]



entry	2	RBr	products 3	yield[b] (%)
1	**2a**	*p*-PhC_6H_4Br	 **3a**	83
2	**2b**	*p*-AcC_6H_4Br	 **3b**	88
3	**2b**	*o*-$MeOC_6H_4Br$	 **3c**	76
4	**2b**	*p*-PhC_6H_4Br	 **3d**	80
5	**2c**	*p*-AcC_6H_4Br	 **3e**	91
6	**2e**	*o*-$MeOC_6H_4Br$	 **3f**	79
7	**2e**	*p*-AcC_6H_4Br	 **3g**	87
8	**2f**	*p*-AcC_6H_4Br	 **3h**	86

[a] 1.2 mmol of potassium cyclopropyl trifluoroborate, 1.0 mmol of aryl bromides, 2 mol % of $Pd(PPh_3)_4$, 3.0 equiv of K_3PO_4·$3H_2O$, 4.0 mL of toluene−water (3:1, v: v), reflux for 20 h. [b] Isolated yields based on aryl bromides used.

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bromides containing an electron-withdrawing group (Table 3, entries 2, 5, 7, and 8) but also with the ones bearing electron-donating groups (Table 3, entries 1,3, 4, and 6). The 2D NOESY spectra of **3** showed that the products had the same configurations as the potassium cyclopropyl trifluoroborates **2** used.

In summary, stereodefined potassium cyclopropyl trifluoroborates were prepared for the first time by the cyclopropanation of the alkenylboronic esters of pinacol generated from the corresponding alkenylboronic acids and pinacol in the presence of anhydrous $MgSO_4$, followed by in situ treatment with KHF_2 in high yields. The first Suzuki−Miyaura cross-coupling reaction of potassium cyclopropyl trifluoroborates with aryl bromides under appropriate conditions has also been achieved in satisfactory yields. In the coupling reaction, the configurations of the cyclopropanes were retained.

In addition, potassium cyclopropyl trifluoroborates are monomeric and stable in air and are easily purified, stored, and handled. Thus, this work provides a new and facile approach to synthesize various stereodefined cyclopropylarenes, and it promises to be a potentially facile method for the synthesis of enantiomerically pure cyclopropanes. Further studies on the application of this method in the synthesis of enantiomerically pure cyclopropanes are currently underway in our laboratory.

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Supporting Information Available: Experimental details and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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