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A Novel Stereocontrolled Synthesis of 1,2-*trans* Cyclopropyl Ketones via Suzuki-Type Coupling of Acid Chlorides with Cyclopropylboronic Acids

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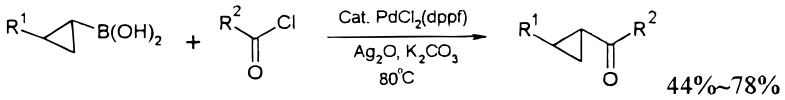
ABSTRACT



The palladium-catalyzed cross-coupling reaction of cyclopropylboronic acids with acyl chlorides was achieved by the combination of Ag_2O and K_2CO_3 as the base. Highly enantiomerically enriched cyclopropyl ketones (ee >90%) were also obtained by the reaction of corresponding chiral cyclopropylboronic acids.

The cyclopropyl ketone moiety is not only recognized to exhibit important properties in mechanistic studies[1] but it is also found in a growing class of natural products isolated from a wide spectrum of marine organisms with important physiological properties.[2] The general methods used for the synthesis of cyclopropyl ketones are the cyclopropanation of α,β-unsaturated ketones, or its derivatives by diverse reagents,[3] and the reaction of cyclopropane carboxylic acid chlorides with organometallic reagents.[4] The cross-coupling of acid chlorides with cyclopropyltin and zinc reagents in the presence or absence of a palladium catalyst also affords cyclopropyl ketones.[5] Despite the many existing strategies for the construction of cyclopropyl ketones, new and effective methods for stereocontrolled substituted cyclopropyl ketones are still sought. Herein we wish to report a novel approach to the synthesis of *trans*-2-substituted cyclopropyl ketones by Suzuki-type coupling of acid chlorides with cyclopropylboronic acids.

A wide range of aryl and 1-alkenylborane reagents undergo the palladium-catalyzed cross-coupling reaction with alkyl, allylic, alkenyl, aryl, and alkynyl substrates.[6] However, there are only limited reports about the couplings of arylboron compounds with acid chlorides in the literature. In 1993 Uemura reported the Suzuki-type cross-coupling of acid chlorides and sodium tetraphenylborate.[7] More recently, Bumagin and Haddach also reported the Suzuki−Miyaura-type coupling of arylboronic acids with acid chlorides under different conditions.[8] However, the coupling of alkylboronic acids with acid chlorides has not been described. Recently the coupling reactions of cyclopropylboronic acids have attracted increasing interest,[9] because the cyclopropylboronic acids are available by the stereodefined cyclopropanation of

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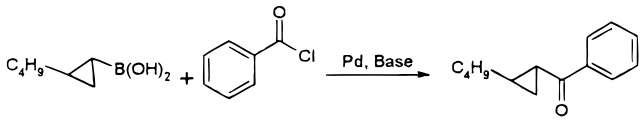
the corresponding alkenylboronic acids (esters).[10] They are highly stable in air and are easily purified by recrystallization from water. In addition, enantiomerically enriched cyclopropylboronic acids can readily be obtained by the cyclopropanation of the corresponding alkenylboronic acid esters with the appropriate chiral auxiliaries.[11] Our group has investigated the cross-coupling of cyclopropylboronic acids with aryl halides[9b] and bromoacrylates.[9d] We now report a new synthesis of stereodefined cyclopropyl ketones (Scheme 1).

Scheme 1



1a **2a** **3aa**

We first studied the coupling of *trans*-1,2-butylcyclopropylboronic acid with benzoyl chloride under Bumagin's conditions, using 3% $PdCl_2$ as the catalyst in acetone−water (3:1) and Na_2CO_3 as the base.[8a] Unfortunately, the desired product was not detected (Table 1, entry 1). This is probably due to the slow transmetalation between the cyclopropylboronic acids and RCOPdCl species, because of the low nucleophilicity of the cyclopropyl group on the boron. The use of Cs_2CO_3 as the base (Haddach's condition[8b]) also did not make the coupling reaction take place (Table 1, entry 2). The fact that Ag_2O dramatically enhances the rate of some coupling reactions[12] encouraged us to use it to active the reaction. As expected, the coupling reaction of cyclopropylboronic acid with benzoyl chloride occurred when Ag_2O was employed as the base, albeit in lower yield (Table 1, entry 3).

When the reaction was carried out with Ag_2O and other bases (Cs_2CO_3 or KOH), the reaction yields were improved (entries 4 and 5). After further screening, it was found that the combination of Ag_2O and K_2CO_3 in a nonpolar solvent led to a facile cross-coupling reaction (entry 6), but in a polar solvent (dioxane) the reaction was sluggish (entry 7). We believe that Ag_2O may play an important role in accelerating the transmetalation between cyclopropylboronic acids and the RCOPdCl species.

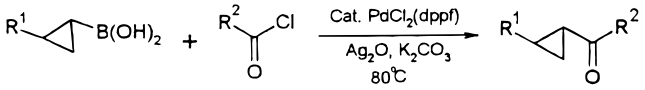
The reactions of various acid chlorides with cyclopropylboronic acids were explored under the optimized reaction conditions; the results are collected in Table 2.

Table 1. Effect of the Bases and Solvents on the Coupling Reaction of *trans*-Butylcyclopropylboronic Acid with Benzoyl Chloride[a]

entry	conditions	yield, %[b]
1	acetone−water (3:1), Na_2CO_3, 3%$PdCl_2$	*c*
2	toluene, Cs_2CO_3, 3% $Pd(PPh_3)_4$	*c*
3	toluene, Ag_2O, 3% $PdCl_2$(dppf)	15
4	toluene, Ag_2O, Cs_2CO_3, 3% $PdCl_2$(dppf)	35
5	toluene, Ag_2O, KOH, 3%$PdCl_2$ (dppf)	40
6	toluene, Ag_2O, K_2CO_3, 3% $PdCl_2$(dppf)	78
7	dioxane, Ag_2O, K_2CO_3, 3% $PdCl_2$(dppf)	30

[a] All reactions were carried out using a mixture of *trans*-2-butylcyclopopylboronic acid (1.0 mmol), benzoyl chloride (2.0 mmol), 3% catalyst, and base (2 equiv) in 4 mL of solvent, for 16 h, at 80 °C (except for entry 1) under a nitrogen atmosphere. [b] Yields of isolated product based on the amount of *trans*-2-butylcyclopopylboronic acid used. [c] Unreacted *trans*-2-butylcyclopopylboronic acid was obtained in these cases.

Table 2. Ag_2O-Assisted, Palladium-Catalyzed Cross-Coupling Reactions of Cyclopropylboronic Acid with Various Acid Chlorides[a]



1 **2** **3**

entry	**1**, R^1 =	**2**, R^2 =	yield, % (**3**)[b]
1	*n*-C_4H_9 (**1a**)	**2a**	78 (**3aa**)
2	*n*-C_6H_{13} (**1b**)	4-MeC_6H_4 (**2b**)	75 (**3bb**)
3	**1a**	2-$MeOC_6H_4$ (**2c**)	77 (**3ac**)
4	**1a**	3-$MeOC_6H_4$ (**2d**)	76 (**3ad**)
5	**1b**	4-$MeOC_6H_4$ (**2e**)	70 (**3be**)
6	**1b**	2-FC_6H_4 (**2f**)	64 (**3bf**)
7	**1b**	2,4-$2FC_6H_3$ (**2g**)	60 (**3bg**)
8	**1b**	3-$CF_3C_6H_4$ (**2p**)	64 (**3bp**)
9	**1b**	4-$BuOC_6H_4$ (**2q**)	74 (**3bq**)
10	**1b**	4-$EtOC_6H_4$ (**2h**)	75 (**3bh**)
11	**1a**	3-CNC_6H_4 (**2i**)	59 (**3ai**)
12	**1a**	4-PhC_6H_4 (**2j**)	69 (**3aj**)
13	**1a**	2-naphthyl (**2k**)	70 (**3ak**)
14	**1b**	2-naphthyl (**2k**)	59 (**3bk**)
15	**1b**	2,6-$2ClC_6H_3$ (**2l**)	*c*
16	**1b**	2,4,6-$3MeOC_6H_2$ (**2m**)	*c*
17	*n*-C_5H_{11} (**1c**)	2-thiophene-yl (**2n**)	49 (**3cn**)[d]
18	**1c**	2-furyl (**2o**)	45 (**3co**)[d]
19	**1a**	**2o**	44 (**3ao**)[d]
21	**1a**	**2n**	51 (**3an**)[d]

[a] All the reactions were carried out using a mixture of cyclopropylboronic acids (1.0 mmol) and acid chlorides (2 mmol), 2 equiv of Ag_2O, 2 equiv of K_2CO_3 (based on boronic acids), and 3% $PdCl_2$(dppf) in 4 mL of toluene at 80 °C under a nitrogen atmosphere for 12−16 h. All the products were identified by ^1H NMR, IR, and mass spectral and elemental analysis or HRMS and ^{13}C NMR. [b] On the basis of the amount of cyclopopylboronic acids used. [c] Unreacted cyclopopylboronic acid was recovered in these cases. [d] Reactions were carried out for 24 h.

As shown in Table 2, the cross-coupling reaction of *trans*-2-alkylcyclopropylboronic acids with various acid chlorides proceeded readily (except for entries 15 and 16) with satisfactory yields. It is important to note that substituents on the acid chlorides did not significantly affect the coupling

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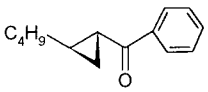
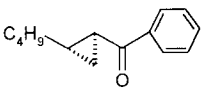
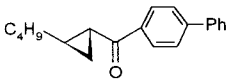
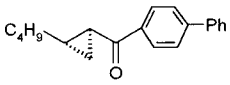
Table 3. Synthesis of Enantiomerically Enriched Cyclopropyl Ketones by the Coupling Reaction of the Chiral Cyclopropylboronic Acids with Acid Chlorides[a]

entry	chiral auxiliary	chiral cyclopropyl-boronic acids[b]	products	$[\alpha]^{20}_D$ (in $CHCl_3$)	yield (%)[c]	ee (%)
1	(+)-TMTA	 ee % = 90% (*R*, *R*)-**1a**	 (*R*, *R*)-**3aa**	-40.5 (0.8830)	77	92[d]
2	(-)-TMTA	 ee % = 94% (*S*, *S*)-**1a**	 (*S*, *S*)-**3aa**	41.9 (0.9102)	76	95[d]
3	(+)-TMTA	(*R*, *R*)-**1a**	 (*R*, *R*)-**3aj**	-13.1° (1.0333)	71	90[e]
4	(-)-TMTA	(*S*, *S*)-**1a**	 (*S*, *S*)-**3aj**	13.4° (0.7032)	77	94[e]

[a] Coupling reactions were carried out using a mixture of chiral cyclopropylboronic acids (1.0 mmol) and acid chlorides (2 mmol), 2 equiv of Ag_2O, 2 equiv of K_2CO_3 (based on boronic acids), and 3% $PdCl_2$(dppf) in 4 mL of toluene at 80 °C under a nitrogen atmosphere for 12−16 h. [b] The enantiomeric purities were established on the basis of the ee values of the corresponding carbinols generated by the alkali oxidation of the cyclopropylboronic acids. [c] Yields of isolated products based on the cyclopropylboronic acids. [d] Determined by HPLC (Chiralcel AD). [e] Determined by HPLC (Chiralcel OJ).

reaction; the yields of reaction with acid chlorides bearing donating groups were only slightly better than those of acid chlorides bearing withdrawing functions. However, the bulky 2,6-di- or 2,4,6-trisubstituted acid chlorides did not give the desired products (entries 15 and 16). Apparently, the reaction rate is greatly influenced by steric hindrance. Moderate yields of cyclopropyl ketones were obtained with heteroaryl acid chlorides as well (entries 17−21). The ^{1}H NMR spectra of the products and 2D ^{1}H−^{1}H NOESY NMR of products (**3aa**, **3bb**, **3ad**, **3bf**) showed that the configurations of the cyclopropyl groups of their organoboron partner were retained.

The enantiomerically enriched (1*R*,2*R*)-cyclopropylboronic acids can be readily obtained by the asymmetric cyclopropanation of the corresponding (*E*)-alkenylboronic ester with the enantiomerically pure (+)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide, (+)-TMTA, as the chiral auxiliary, followed by the hydrolysis. Similarly, the corresponding (1*S*,2*S*)-isomer was obtained by using (−)-TMTA as the auxiliary. The cross-coupling reaction of acid chlorides with the enantiomerically enriched cyclopropylboronic acids also successfully gave the corresponding cyclopropyl ketones with high ee (Table 3).

Table 3 outlined that the ee values of the coupling products were similar to those of the corresponding cyclopropylboronic acids used. In addition, the reaction of the cyclopropylboronic acid of the same optical purity with different acid chlorides gave the corresponding cross-coupling products with similar optical purities (entries 1 and 3; 2 and 4). All these results suggest that the chirality is retained in the coupling process.

In summary, the first palladium-catalyzed cross-coupling reaction of cyclopropylboronic acids with acid chlorides has been achieved. The addition of Ag_2O and K_2CO_3 as base was found to be essential. As the stereodefined cyclopropylboronic acids and the enantiomerically enriched cyclopropylboronic acids were readily available, the present method provided a new and effective approach to the synthesis of stereodefined cyclopropyl ketones from acid chlorides and cyclopropylboronic acids. Further study on the scope of the reaction is 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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