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Synthesis of β-Boryl-α,β-unsaturated Carbonyl Compounds *via* Palladium-Catalyzed Cross-Coupling Reaction of Bis(pinacolato)diboron with Vinyl Triflates

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Abstract: Cross-coupling reaction of bis(pinacolato)diboron with β-(trifluoromethanesulfonyloxy)-α,β-unsaturated carbonyl compounds was carried out in the presence of $PdCl_2(PPh_3)_2$-$2PPh_3$ (3 mol%) and KOPh in toluene or K_2CO_3 in dioxane for the synthesis of cyclic and acyclic β-boryl-α,β-unsaturated esters, amides, and ketones in high yields.

Key words: diboron, vinyl triflate, palladium, cross-coupling, catalysis

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β-Boryl-α,β-unsaturated carbonyl compounds are attractive synthetic intermediates which allow inter- or intramolecular Diels-Alder reaction,[1] asymmetric dipolar cycloaddition or 1,4-addition,[2] cyclopropanation,[3] and radical addition.[4] Although β-borylacrylates are available *via* hydroboration of propiolic acid esters,[1,5] preparation of the corresponding ketone and aldehyde derivatives requires a multi-step procedure[1,6] and there are few reports for cyclic or polysubstituted derivatives.[7] In connection with our interest in the synthesis of organoboron compounds *via* the cross-coupling reaction of diborons with organic electrophiles[8] including aryl,[8,9] vinyl,[8,10] allyl,[8,11] and benzyl[8,12] halides or triflates, we wish to disclose here a palladium-catalyzed cross-coupling reaction of bis(pinacolato)diboron[13] (pin_2B_2, pin = $Me_4C_2O_2$) (**1**) with vinyl triflates[14] (**2**) to yield the corresponding β-boryl-α,β-unsaturated carbonyl compounds (**3**) (Eq. 1).

<<Eq. 1>>

The effects of bases and solvents on the reaction are shown in Table 1. The conditions previously reported for the coupling of pin_2B_2 **1** with vinyl halides or triflates ($PdCl_2(PPh_3)_2$-$2PPh_3$/KOPh/toluene/50 °C)[10] gave borylated products **3** in high yields for most of the vinyl triflates **2**, but the reaction often resulted in very low yields due to a competitive base-induced side-reaction. For example, the reaction of **1** (1.1 mmol) with ethyl 2-(trifluoromethanesulfonyloxy)-1-cyclopentenecarboxylate (1.0 mmol) in the presence of $PdCl_2(PPh_3)_2$-$2PPh_3$ (0.03 mmol) and KOPh

(1.5 mmol) in toluene (6 ml) at 50 °C resulted in 9% yield (Entry 1). Analysis of the reaction mixture revealed the formation of phenyl triflate (90%) resulted by ester-exchange between the triflate and KOPh.[15] A sterically more hindered 2-MeC_6H_4OK base, which is expected to inhibit the ester-exchange, also produced the corresponding triflate in 69% yield (Entry 2). Alternatively, use of a K_2CO_3 base in dioxane was found to be effective for such substrates sensitive to the phenoxy anion to promote the desired coupling in 67% yield (Entry 3). Although K_2CO_3 was prone to induce further coupling of **3** with **2** giving a dimer of **2** (ca. 30%), stronger bases such as K_3PO_4 further enhanced the dimerization (Entry 4) and weaker bases such as KOAc did not promote the coupling (Entry 5). Use of less-polar solvents such as toluene resulted in low conversion (Entry 6). Although the reactions using K_2CO_3 took longer times at 50 °C, the same reactions were completed at 80 °C within 5 h in dioxane and 24 h in toluene, respectively (Entries 7 and 8).

<<Table 1>>

The palladium-catalyzed cross-coupling of pin_2B_2 **1** with the representative vinyl triflates **2** in the presence of KOPh in toluene at 50 °C (Method A) or K_2CO_3 in dioxane at 80 °C (Method B) is summarized in Table 2.[16] All **2** including cyclic or acyclic ester, amide, and ketone derivatives were converted into the corresponding β-boryl-α,β-unsaturated carbonyl compounds **3** in high yields by either Method A or B. The reactions were faster under the conditions of Method A than those of Method B; however, the yields highly depended upon the substrates. Method A resulted in low yields due to the formation of phenyl triflate (30-90%) for substrates sensitive to the phenoxy anion, including five-membered ester (Entry 1), six-membered amide (Entry 5), five-membered ketone (Entry 6), and less-hindered six-membered ketone having no substituent at the α carbon (Entry 8). On the other hand, Method A was a better choice for seven- and eight-membered esters (Entries 3 and 4), and acyclic ester (Entry 10), because Method B resulted in the formation of symmetrical 1,3-dienes (15-30%) arising from dimerization of **2**. The borylation of acyclic ester and amide derivatives of **2** having *E* stereochemistry retained completely the configuration of the double bond to give isomerically pure (*Z*)-**3** in high yields (Entries 10 and 11).

<<Table 2>>

In general, *E* or *Z* configuration of 1-alkenyl halides or triflates can be retained completely in the cross-coupling of organoboron compounds;[17] however, the amide derivative of triflate (*Z*)-**4** unexpectedly provided the borylated product (*Z*)-**5** by Method A and a mixture of (*Z*)-**5** and (*E*)-**5** (64:36) by Method B (Eq. 2). Monitoring of a benzene-d_6 solution of the (*Z*)-**4** or (*E*)-**5** in the presence of $Pd(PPh_3)_4$ and KOPh by ^1H NMR and GC at 50 °C resulted in no conversion into (*E*)-**4** or (*Z*)-**5**, suggesting the isomerization during the catalytic process. It remains unclear which step is responsible for such isomerization; however, a vinylpalladium(II) species generated by

oxidative addition of a vinyl halide or triflate to a palladium(0) complex often undergoes *E*-*Z* isomerization.[18]

<<Eq. 2>>

The direct preparation of β-boryl-α,β-unsaturated carbonyl compounds **3** from pin_2B_2 **1** and the corresponding vinyl triflates **2** now allows a one-pot, two-step procedure for the synthesis of ketone or ester derivatives of unsymmetrical 1,3-dienes **7** (Table 3). The stereoselective syntheses of three dienes **7** were easily achieved in 76%, 76%, and 77% yields when the borylation of **2** (1.1 mmol) with **1** (1.1 mmol) was directly followed by the coupling with another vinyl triflate **6** (1.0 mmol).[19] A combination of $PdCl_2$(dppf) (0.03 mmol) and K_3PO_4 (3.0 mmol) in dioxane at 80 °C was recognized to be the best conditions for the second coupling.[17]

<<Table 3>>

References and Notes

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(16) A representative procedure for **3**: A flask placed with $PdCl_2(PPh_3)_2$ (0.03 mmol), PPh_3 (0.06 mmol), pin_2B_2 **1** (1.1 mmol), and KOPh or K_2CO_3 (1.5 mmol) was flushed with nitrogen. Toluene or dioxane (6 ml) and ethyl 2-(trifluoromethanesulfonyloxy)-1-cyclohexenecarboxylate (1.0 mmol) were then added. The resulting mixture was stirred at 50 °C or 80 °C for the period shown in Table 2. The product was isolated by chromatography over silica gel followed by Kugelrohr distillation to give an analytically pure sample: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.27 (t, 3 H, *J* = 7.2 Hz), 1.33 (s, 12 H), 1.55-1.65 (m, 4 H), 2.20-2.25 (m, 4 H), 4.21 (q, 2 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 14.25, 21.42, 21.85, 24.12, 24.77, 27.93, 60.70, 83.34, 134.24, 169.19; HRMS, Found: *m/z*, 280.1846. Calcd for $C_{15}H_{25}BO_4$: M^+, 280.1846.
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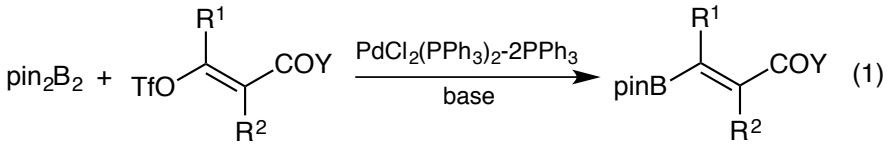
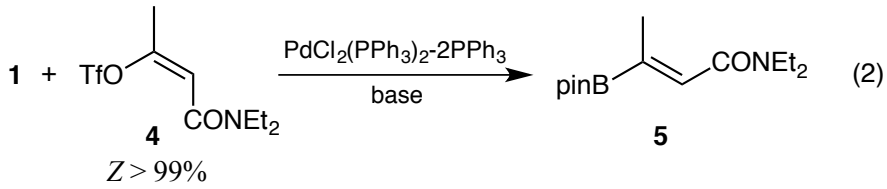
(19) The 1,3-dienes **7** shown in Table 3 could be purified by column chromatography over silica gel to give analytically pure samples.



1 **2** Y = OR, NR_2, R **3** (1)



4 **5** (2)

Z > 99%

KOPh/toluene/50 °C/1 h: 88% (*Z* > 99%)
K_2CO_3/dioxane/80 °C/5 h: 91% (*Z* = 64%)

Table 1 Effects of Bases and Solvents[a]

Entry	Base/Solvent	Temp/°C	Time/h	Yield/%[b]
1	KOPh/toluene	50	2	9[c]
2	2-MeC_6H_4OK/toluene	50	2	4[d]
3	K_2CO_3/dioxane	50	16	67[e]
4	K_3PO_4/dioxane	50	16	58[e]
5	KOAc/dioxane	50	16	4
6	K_2CO_3/toluene	50	16	1
7	K_2CO_3/dioxane	80	5	67[e]
8	K_2CO_3/toluene	80	24	65[e]

[a]The coupling reaction of diboron **1** (1.1 mmol) with ethyl 2-(trifluoromethanesulfonyloxy)-1-cyclopentenecarboxylate (1.0 mmol) was carried out in the presence of $PdCl_2(PPh_3)_2$ (0.03 mmol), PPh_3 (0.06 mmol), and base (1.5 mmol) in 6 ml of solvent.

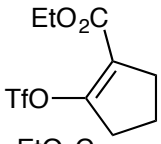
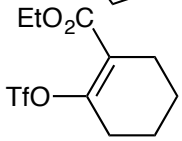
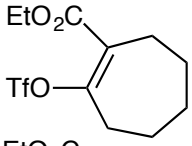
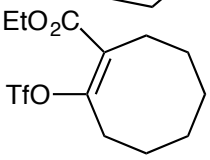
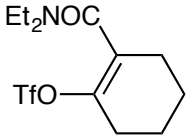
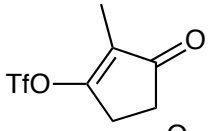
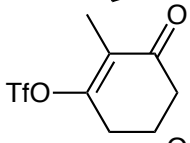
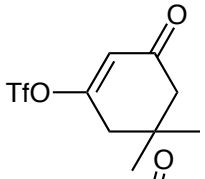
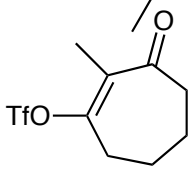
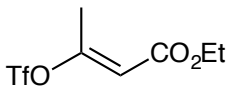
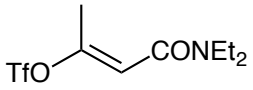
[b]GC yields based on the triflate.

[c]The reaction accompanied PhOTf (90%).

[d]The reaction produced 2-MeC_6H_4OTf (69%)

[e]The reactions gave a dimer of the triflate (30-40%).

Table 2 Synthesis of 1-Alkenylboronates **3** (Eq. 1)[a]

Entry	Triflate **2**	Yield/%[b]	
		Method A[c]	Method B[d]
1		9 (2 h)	67 (5 h)
2		78 (1 h)	91 (6 h)
3		76 (1 h)	74 (3 h)
4		72 (1 h)	60 (5 h)
5		60 (6 h)	98 (3 h)
6		21 (1 h)	78 (2 h)
7		81 (2 h)	91 (5 h)
8		25 (2 h)	78 (2 h)
9		72 (1 h)	77 (3 h)
10		93 (1 h)	72 (3 h)
11		75 (1 h)	76 (2 h)

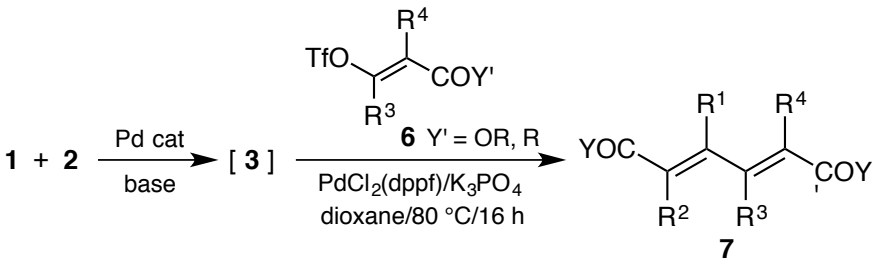
[a]All reactions were conducted by using diboron **1** (1.1 mmol), triflate **2** (1.0 mmol), $PdCl_2(PPh_3)_2$ (0.03 mmol), PPh_3 (0.06 mmol), base (1.5 mmol), and solvent (6 ml).

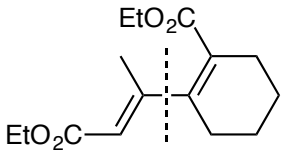
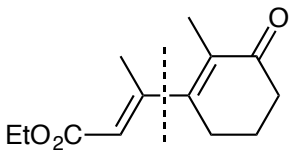
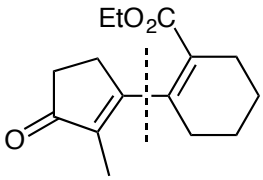
[b]GC yields based on triflates **2**.

[c]Method A: KOPh/toluene/50 °C.

[d]Method B: K_2CO_3/dioxane/80 °C.

Table 3 One-Pot Synthesis of 1,3-Dienes **7**[a]



Entry	1,3-Diene **7**[b]	Yield/%[c]
1		76[d]
2		76
3		77

[a]To a solution of 1-alkenylboronate **3** resulted by the reaction of diboron **1** (1.1 mmol) with triflate **2** (1.1 mmol) in toluene or dioxane (4 ml) were added second triflate **6** (1.0 mmol), $PdCl_2$(dppf) (0.03 mmol), K_3PO_4 (3.0 mmol), and dioxane (4 ml), and the mixture was stirred at 80 °C for 16 h.

[b]Left part of dotted line comes from **2** and right part from **6**.

[c]Isolated yields based on triflates **6**.

[d]GC yield after 5 h.

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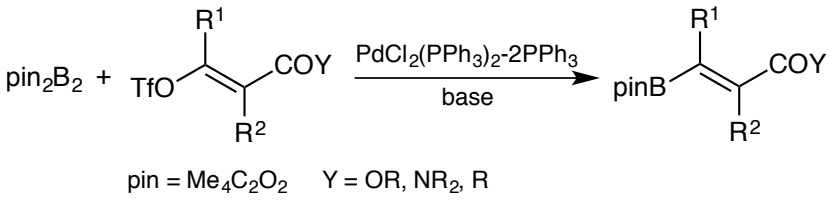

pin = $Me_4C_2O_2$ Y = OR, NR_2, R