A Sequence of Palladium-Catalyzed Borylation of Allyl Acetates with Bis(pinacolato)diboron and Intramolecular Allylboration for the Cyclization of Oxo-2-alkenyl Acetates

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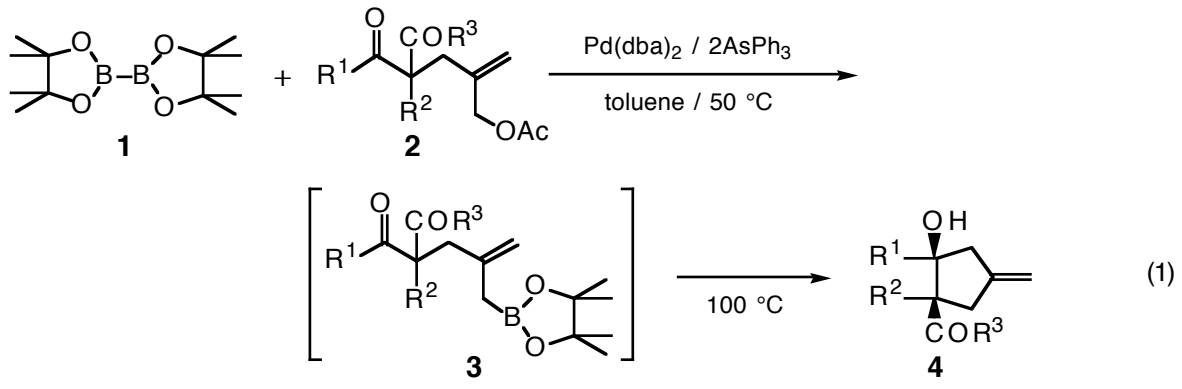
Abstract: *The cross-coupling reaction of bis(pinacolato)diboron with oxo-2-alkenyl acetates at 50 °C in the presence of $Pd(dba)_2$-$2AsPh_3$ (3 mol%) in toluene followed by intramolecular allylboration reaction at 100 °C produced the stereodefined cyclic homoallyl alcohols in good to excellent yields.*

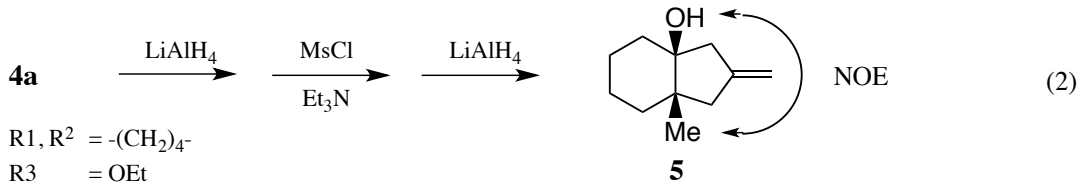
Intramolecular addition reaction of allylmetals to carbonyl substrates is a powerful tool for the synthesis of cyclic homoallyl alcohols with defined regio- and stereochemistry. Extensive studies have been made on Lewis acid- or fluoride anion-promoted cyclization of oxo-2-alkenylsilanes[1] or -stannanes[2] and Barier type reductive cyclization of oxo-2-alkenyl halides induced by Mg,[3] In,[4] and SmI_2.[5] In contrast to these, the corresponding reaction of allylboranes has not been well developed mainly due to the lack of general method for introduction of boryl group into carbonyl substrates.[6] Recently, we reported the regio- and stereoselective synthesis of allylboron compounds by the palladium(0)-catalyzed cross-coupling reaction of bis(pinacolato)diboron (**1**) with allyl acetates.[7] Since a variety of allyl acetates are easily available from corresponding alcohols and the reaction conditions are sufficiently mild ($Pd(dba)_2$-DMSO-50°C), the method may provide an efficient and convenient access to functionalized allyboranes. In order to demonstrate the synthetic utility of this method, we examined the synthesis of oxo-2-alkenylboranes (**3**) by the cross-coupling of **1** with oxo-2-alkenyl acetates (**2**) and their cyclization to cyclic homoallyl alcohols (**4**) (Eq. 1).



(1)

The sequential reaction, cross-coupling between **1** (1.1.mmol) and ethyl 1-[2-(acetoxy)methyl-2-propenyl]-2-cyclohexanonecarboxylate **2a** (R^1, R^2 = -$(CH_2)_4$-, R^3 = OEt) (1.0 mmol) followed by intramolecular allyboration, was investigated under various conditions. When the coupling was carried out at 50 °C for 16 h with $Pd(dba)_2$-2$AsPh_3$ (3 mol%) in toluene and subsequent cyclization was conducted at 100 °C for 24 h, the desired cyclic homoallyl alcohol **4a** was obtained in the best yield (88%). Both solvent and ligand of palladium played important role at the coupling step. A combination of $Pd(dba)_2$ and DMSO exhibited excellent catalytic activity as reported previously, but the similar reaction in toluene did not proceed because of the catalyst decomposition precipitating palladium black. In such cases, the addition of $AsPh_3$ or PPh_3 is effective to stabilize the active palladium(0) species. Although dppf have been efficiently utilized in the cross-coupling of **1** with aryl halides and triflates,[8] this ligand did not give any satisfactory results. The cyclization step is also affected by the nature of solvent. The reaction was extremely slow when using DMSO presumably due to its coordination to boron center of **3a**, resulting in only 63% yield even at 120 °C (24 h). Less polar solvents are favorable to accelerate the cyclization step.

The ^1H NMR spectra of **4a** in $CDCl_3$ shows a down-field resonance at 3.74 ppm for the hydroxyl proton caused by intramolecular hydrogen bonding between the OH and C=O, clearly indicating *cis*-ring junction of **4a**. The *cis*-cyclization is also supported by NOE experiments of **5** derived from **4a**; the irradiation of the hydroxyl proton at 4.14 ppm in DMSO-d_6 resulted in 2.3% enhancement of the methyl signal at 0.91 ppm (Eq. 2).



(2)

The representative results of the intramolecular allylboration of oxo-2-alkenylboronates **3** generated *in situ* by the cross-coupling of **1** with **2** are summarized in Table 1. A variety of oxo-2-alkenyl acetates **2** smoothly underwent the cross-coupling–cyclization reaction under the conditions optimized above to produce the corresponding cyclic homoallyl alcohols **4** in good to high yields. The 5-5, 6-5, and 7-5 *cis*-fused alcohols **4a**-**4d** were readily obtained by the reaction of acetates **2a**-**2d** derived from cyclic b-ketoesters and diketone (Entries 1-4). The *cis*-ring junction of **4d** was immediately established by the presence of NOE enhancement between methyl protons and hydroxyl proton in ^1H NMR. The reaction of **2e** and **2f** derived from acyclic b-ketoester and diketone afforded monocyclic alcohols **4e** and **4f**, respectively (Entries 5 and 6). Detailed ^1H NMR studies for **4e** revealed that the relative stereochemistry between OH and CO_2Et is *cis*; The spectra exhibit a down-field resonance for the hydroxyl proton and strong NOE enhancement was observed between two methyl groups. Spirocyclic alcohols **4g** was also obtained by the reaction of **2g**, while the yield of the product was somewhat low (Entry 7).

*The representative procedure for **4***: A dry 25-ml flask equipped with a magnetic stirring bar, a septum inlet, an oil bubbler, and a reflux condenser was charged with $Pd(dba)_2$ (dba is dibenzylideneacetone) (0.03 mmol), $AsPh_3$ (0.06 mmol), and toluene (6 ml) under nitrogen. After being stirred at room temperature for 30 min, **1** (1.1 mmol) and **2** (1.0 mmol) were successively

added. The mixture was heated at 50 °C for 16 h and then at 100 °C for 24 h. The resulting mixture was treated with saturated ammonium chloride solution (10 ml) at room temperature for 1 h, extracted with ether (10 ml, three times), and dried over anhydrous magnesium sulfate. An analytically pure product was isolated by column chromatography over silica gel. **4a**: IR (film) 3500, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 1.15-1.45 (m, 3 H), 1.28 (t, 3 H, *J* = 7.1 Hz), 1.54 (dt, 1 H, *J* = 3.58 and 13.3 Hz), 1.70-1.75 (m, 1 H), 1.82 (dd, 2 H, *J* = 4.0 and 9.6 Hz), 2.02 (d, 1 H, *J* = 12.7 Hz), 2.32 (t, 2 H, *J* = 15.7 Hz), 2.69 (dt, 1 H, *J* = 2.5 and 17.6 Hz), 2.99 (dd, 1 H, *J* = 2.6 and 16.5 Hz), 3.74 (d, 1 H, *J* = 2.0 Hz), 4.19 (dq, 2 H, *J* = 1.8 Hz and 7.1 Hz), 4.95 (s, 1 H), 4.99 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 14.10, 22.81, 23.65, 33.22, 34.05, 41.79, 42.18, 55.17, 60.58, 80.31, 108.80, 146.45, 176.74; exact mass calcd for $C_{13}H_{20}O_3$ 224.1413, found 224.1404.

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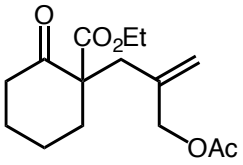
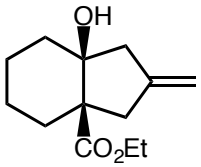
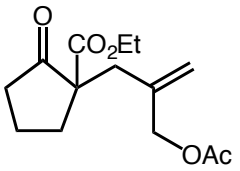
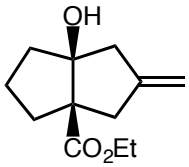
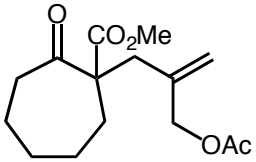
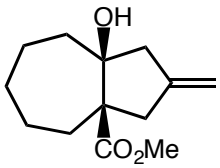
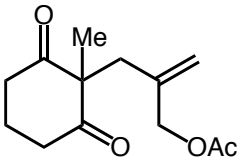
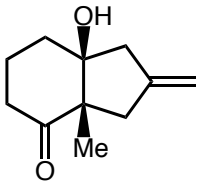
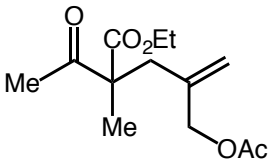
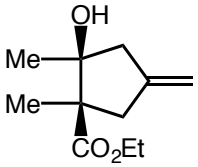
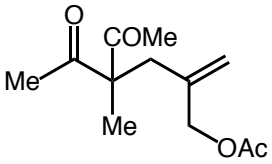
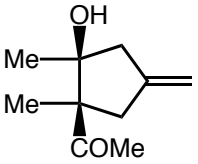
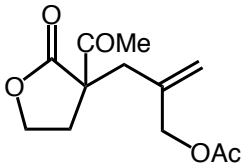
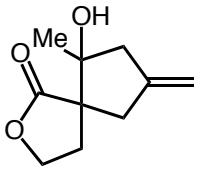
Table 1. The Synthesis of Cyclic Homoallyl Alcohols (Eq. 1)[a]

Entry	Acetate (**2**)		Product (**4**)[b]		Yield / %[c]
1		**2a**		**4a**	72 (88)
2		**2b**		**4b**	82
3		**2c**		**4c**	71
4		**2d**		**4d**	77
5		**2e**		**4e**	62
6		**2f**		**4f**	71
7		**2g**		**4g**	52

a Cross-coupling of **1** (1.1 mmol) with **2** (1.0 mmol) was carried out at 50 °C for 16 h by using $Pd(dba)_2$ (0.03 mmol), $AsPh_3$ (0.06 mmol), and toluene (6 ml) followed by intramolecular allylboration at 100 °C for 24 h.

[b] Stereochemistry of **4** was determined by ^1H NMR analyses.

[c] Isolated yields based on **2** and GLC yield was in parenthesis.

A STEREOSELECTIVE SYNTHESIS OF CYCLIC HOMOALLYL ALCOHOLS VIA THE CROSS-COUPLING REACTION OF DIBORON REAGENT WITH OXO-2-ALKENYL ACETATES: A DIRECT BORYLATION-INTRAMOLECULAR ALLYLBORATION SEQUENCE

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