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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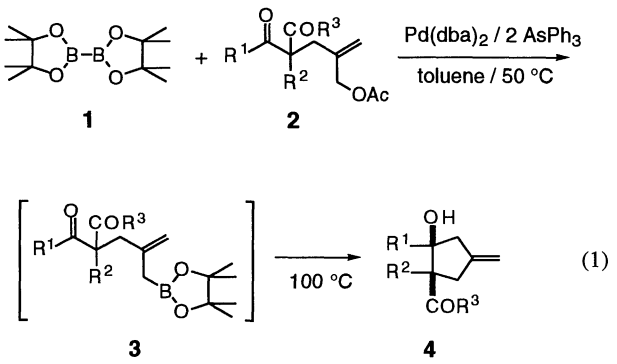
(Received May 12, 1997; CL-970353)

The cross-coupling reaction of bis(pinacolato)diboron with oxo-2-alkenyl acetates in toluene at 50 ℃ in the presence of $Pd(dba)_2$/2 $AsPh_3$ (3 mol%) to give allylboronates was followed by the intramolecular allylboration at 100 ℃. The sequence provided cyclic homoallyl alcohols in high yields.

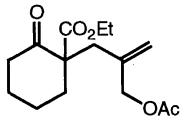
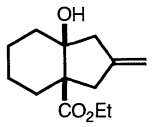
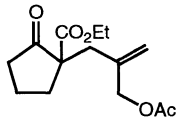
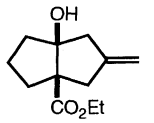
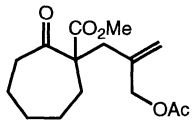
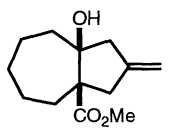
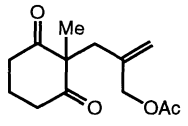
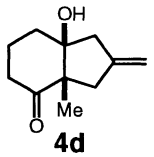
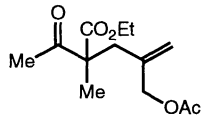
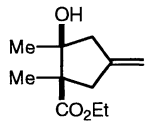
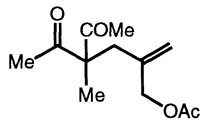
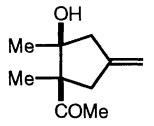
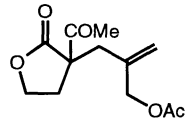
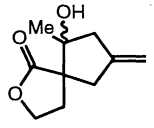
Intramolecular addition of allylmetal reagents to carbonyl substrates is a powerful tool for the synthesis of cyclic homoallyl alcohols with high regio- and stereoselectivity. Lewis acid- or fluoride anion-promoted cyclization of oxo-2-alkenylsilanes[1] or -stannanes,[2] and Barbier type reductive cyclization of oxo-2-alkenyl halides by the use of Mg,[3] In,[4] and SmI_2[5] have been extensively studied. However, the corresponding reaction of allylboranes has not been well developed mainly due to the lack of a general method for introduction of a boryl group into carbonyl substrates.[6] Recently, we reported the regio- and stereoselective synthesis of allylboron reagents by the palladium(0)-catalyzed cross-coupling reaction of bis(pinacolato)diboron (**1**) with allyl acetates.[7] The method provides an efficient and convenient access to variously functionalized allyboranes because a variety of allyl acetates are easily available and the reaction conditions for the coupling are sufficiently mild ($Pd(dba)_2$/DMSO/50℃). In the present paper, we wish to report the direct 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 2 3 4 (1)

The sequential reaction, involving the cross-coupling between **1** (1.1 mmol) and **2a** (R^1, R^2 = -$(CH_2)_4$-, R^3 = OEt, Entry 1 in Table 1) (1.0 mmol) and the intramolecular allylboration, was investigated under various conditions. The best yield was achieved (**4a**, 88%) in toluene when the coupling with $Pd(dba)_2$/2 $AsPh_3$ (dba is dibenzylideneacetone) (3 mol%) at 50 ℃ for 16 h was followed by the cyclization at 100 ℃ for 24 h. Although we have previously reported that $Pd(dba)_2$ in DMSO exhibits excelient catalytic activity in the cross-coupling of **1** with allyl acetates, the intramolecular allylboration of the carbonyl was extremely slow in this solvent, presumably due to its coordination to the boron atom (63%, 120 ℃/24 h). Thus, less polar solvents

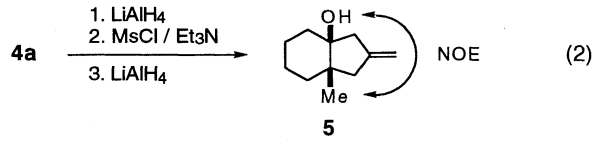
Table 1. Synthesis of **4** (Eq. 1)[a]

Entry	Acetate (**2**)	Product (**4**)	Yield / %[b]
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]The experimental procedures, see the text.
[b]Isolated yields based on **2** and GLC yield in parenthesis.

were desirable for the cyclization; however, a similar cross-coupling in toluene was unsuccessful because of the catalyst decomposition precipitating palladium black. Fortunately, the addition of $AsPh_3$ or PPh_3 (2 equivs) to $Pd(dba)_2$ was found to be effective to stabilize the active palladium(0) species during the cross-coupling at 50 ℃. 1,1'-Bis(diphenylphosphino)ferrocene (dppf) did not give any good results whereas this ligand has been successfully utilized in the coupling of **1** with aryl halides and triflates.[8]

The ^{1}H NMR spectra of **4a** in $CDCl_3$ revealed a down-field resonance at 3.74 ppm for the hydroxyl proton due to the intramolecular hydrogen bonding between OH and C=O, suggesting a *cis*-cyclization. The stereochemistry is further supported by its conversion into **5** and the presence of NOE (2.3 %) in DMSO-d_6 between OH (4.14 ppm) and CH_3 (0.91 ppm) (Eq. 2).



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The representative results are summarized in Table 1. A variety of oxo-2-alkenyl acetates **2** smoothly underwent the cyclization to the corresponding cyclic homoallyl alcohols **4** under the conditions optimized above. The 5-5, 6-5, and 7-5 *cis*-fused alcohols **4a-4d** were readily obtained from cyclic β-ketoesters and diketone (Entries 1-4). Interestingly, acyclic oxo-2-alkenyl acetates, such as **2e** and **2f**, stereoselectively provided a single stereoisomer (**4e** and **4f**) (Entries 5 and 6). ^{1}H NMR analyses of **4e,f** exhibited a down-field resonance for the hydroxyl proton and NOE (1.4%) between two methyl groups.[9] Spirocyclic alcohols **4g** was similarly obtained as a mixture of two stereoisomers (Entry 7).

The representative procedure: 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 **2a** (1.0 mmol) were successively added. The mixture was heated at 50 ℃ for 16 h and then at 100 ℃ 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}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15-1.45 (m, 3 H), 1.28 (t, 3 H, J = 7.1 Hz), 1.54 (dt, 1 H, J = 3.6 and 13.2 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, $CDCl_3$) δ 14.10, 22.28, 23.65, 33.22, 34.05, 41.79, 42.18, 55.17, 60.58, 80.31, 108.80, 146.45, 176.74.

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