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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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)₂-2AsPh₃ (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-alkenylsilanes¹ or -stannanes² and Barier type reductive cyclization of oxo-2-alkenyl halides induced by Mg,³ In,⁴ and SmI₂.⁵ 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 allylboranes. 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).

\[ \begin{align*}
\text{Pd(dba)₂ / 2AsPh₃} & \quad \text{toluene / 50 °C} \\
\text{R¹COR}^{\text{R²}} & \quad \text{R¹COR}^{\text{R²}} \\
\text{R¹COR}^{\text{R²}} & \quad \text{R¹COR}^{\text{R²}} \\
\text{R¹COR}^{\text{R²}} & \quad \text{R¹COR}^{\text{R²}} \\
\text{R¹COR}^{\text{R²}} & \quad \text{R¹COR}^{\text{R²}} \\
\end{align*} \]
The sequential reaction, cross-coupling between 1 (1.1 mmol) and ethyl 1-[2-(acetoxy)methyl-2-propenyl]-2-cyclohexanone carboxylate 2a (R¹, R² = -(CH₂)₄⁻, R³ = OEt) (1.0 mmol) followed by intramolecular allylboronation, was investigated under various conditions. When the coupling was carried out at 50 °C for 16 h with Pd(dba)₂·2AsPh₃ (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 AsPh₃ or PPh₃ is effective to stabilize the active palladium(0) species. Although dpdf have been efficiently utilized in the cross-coupling of 1 with aryl halides and triflates, 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 CDCl₃ 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-d₆ resulted in 2.3% enhancement of the methyl signal at 0.91 ppm (Eq. 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 CO₂Et 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), AsPh₃ (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, CDCl₃) 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); 13C NMR (100 MHz, CDCl₃) 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 C₁₃H₂₀O₃ 224.1413, found 224.1404.

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<sup>a</sup> 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)<sub>2</sub> (0.03 mmol), AsPh<sub>3</sub> (0.06 mmol), and toluene (6 ml) followed by intramolecular allylboration at 100 °C for 24 h.

<sup>b</sup> Stereochemistry of 4 was determined by <sup>1</sup>H NMR analyses.

<sup>c</sup> 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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$$\text{B-B} \quad + \quad \text{COR}^3_{\text{R2}} \quad \xrightarrow{\text{Pd(dba)}_2/2\text{AsPh}_3} \quad \text{toluene / 50 °C} \quad \rightarrow \quad \text{OH} \quad \text{COR}^3_{\text{R2}}$$