Synthesis of Oxo-2-alkenylboronates and their Cyclization to 3-Methylene Cycloalkanols *via* Intramolecular Allylboration

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The cross-coupling reaction between halocarbonyl compounds with Knochel's (dialkoxyboryl)methylzinc reagent provided a new synthesis of oxoalk-2-enylboronates; the *in situ* cyclization of these boronates gave 3-methylene cyclopentanols or cycloheptanols in high yields.

Allylboration of aldehydes and ketones with allylic boron reagents and the use of the resulting homoallylic alcohols in the synthesis of complex molecules have been amply demonstrated by several groups.[1] The allylic boron compounds are most conveniently prepared by the reaction of allyl-magnesium or -lithium reagents with alkoxy- or halo-boranes.[2] Although these approaches have been successfully applied for the synthesis of a variety of allylic boronates, they suffer from a general lack of regio- and stereo-selectivity as well as inability to include functional groups sensitive to the magnesium or lithium reagent. Thus, the synthesis of oxo-2-alkenylboronates **3**, which was required for intramolecular allylboration, has not been reported until very recently;[3,4] whereas the similar intramolecular allylmetallation reaction is well documented for other organometallics.[5] We previously reported that the cross-coupling reaction of 1-haloalk-1-enes with Knochel's (dialkoxyboryl)methylzinc reagent **2**[6] provided allylic boronates stereoselectively.[4] The zinc reagents tolerate many functional groups including ketone and aldehyde carbonyls so that the reaction may provide a direct and simple procedure for the synthesis of allylic boronates having a carbonyl group in the same molecule. We report here the first successful intramolecular allylboration reaction of such oxoallylboronates generated *in situ* by the palladium-catalysed cross-coupling reaction of halocarbonyl compounds **1** with **2** [eqn. (1)].

Table 1 Reaction conditions[a] with 1.5 equiv. of **2**

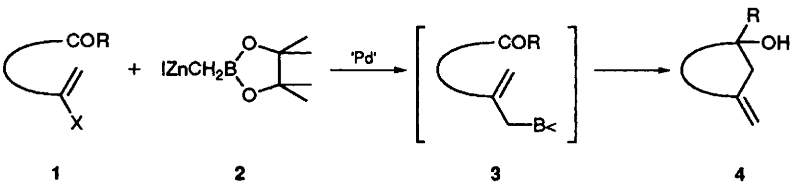
Entry	Solvent	Catalyst	Yield (%)[b]
1	dioxane	Pd(PPh$_3$)$_4$	70 (67)
2		Pd(DBA)$_2$/4AsPh$_3$[d]	76
3		Cl$_2$Pd(PPh)$_2$	37
4		Pd(OAc)$_2$/3PPh$_3$	86
5		Pd(OAc)$_2$/4PPh$_3$	59
6	benzene	Pd(OAc)$_2$/3PPh$_3$	87 (78)
7	DMF	Pd(OAc)$_2$/3PPh$_3$	74
8	THF	Pd(OAc)$_2$/3PPh$_3$	0[c]

[a] All reactions were carried out at 70 °C for 3 h using 1-(2-bromoprop-2-enyl)cyclohexanecarbaldehyde (1 mmol), **2** (1.5 mmol) and Pd catalyst (3 mol%), unless otherwise noted. [b] GLC yields and isolated yields are shown in parentheses. [c] At 50 °C for 5 h. [d] DBA = dibenzylideneacetone.

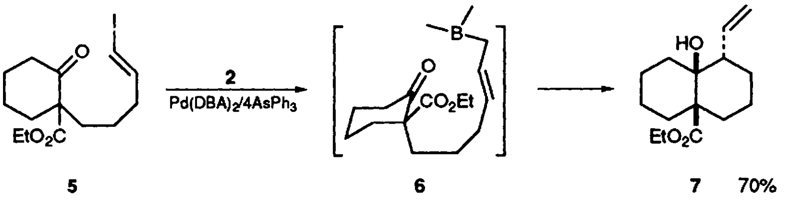
The reaction conditions are summarized in Table 1. The reaction directly provided a spirocyclic alcohol by subsequent intramolecular allylboration (the reaction shown as entry 2, Table 2). All the palladium complexes examined were found to be effective, but the use of 3 equiv. of triphenylphosphine with palladium acetate was recognized to be more effective than tetrakis(triphenylphosphine)palladium(0) (entries 1 and 4–7). The less phosphine palladium complexes may be effective in keeping the decomposition of the thermally unstable borylmethylzinc reagent or enolization of carbonyl compounds to a minimum by improvement of the coupling rate through their high tendency to undergo oxidative addition. Intermolecular allylboration with pinacol borates is rather slow due to steric bulkiness; however, the intramolecular reaction proceeded readily under conditions for the cross coupling at 70 °C.

In Table 2, the representative results of the intramolecular allylboration reaction of oxo-2-alkenylboronates generated *in situ* by cross-coupling reaction with **2** are summarized. We obtained keto-2-bromoalkenes, the key precursors for this palladium-catalysed cyclization, by the improved procedure[7] for the alkylation of ketoesters with 2,3-dibromopropene[8] or 2-bromo-5-iodopentane[9] (entries 4, 6, and 7). Stork's procedure[10] for the alkylation of cyclohexylimine of aldehydes with these bromoalkenes provided high yields of aldehyde precursors for spiroannulation (entries 2 and 3). Treating these bromides with **2** in the presence of a palladium catalyst produced the corresponding five- and seven-membered exomethylene spirocyclic or bicyclic alcohols in high yields. However, the synthesis of a (5 + 7) bicyclic compound resulted in an unexpected diene, presumably due to the formation of a lactone and subsequent elimination of carbon dioxide suggesting the stereoselective formation of a *cis*-annulated intermediate (entry 7).

The cyclization reaction should be highly valuable if the new ring can be generated with defined stereochemistry. We chose the terminal *E*-iodoalkene **5** as a substrate to study stereoselectivity in cyclization, and its reaction was carried out in benzene at 70 °C for 16 h in the presence of **2** (1.5 equiv.), Pd(DBA) (3 mol%), and Ph$_3$As (12 mol%) [eqn. (2)]. ^{13}C and ^{1}H NMR (400 MHz) spectra revealed that the addition reaction of *E*-allylboronate intermediate proceeded to produce a *trans*-homoallylic alcohol with high diastereoselectivity over 99% **7**.† The stereoselectivity of intramolecular allylbor-

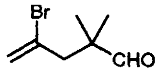
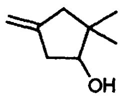
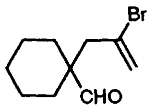
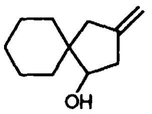
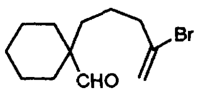
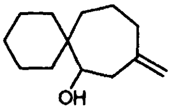
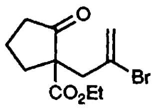
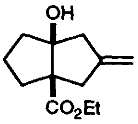
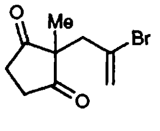
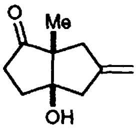
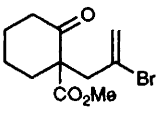
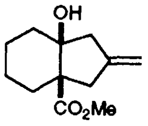
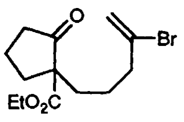
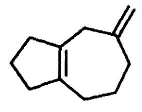


(1)



(2)

Table 2 Synthesis of cyclic homoallyl alcohols[a]

Entry	Halocarbonyl cpd.	Catalyst	Product	Yield/%[b]
1		Pd(OAc)$_2$/3PPh$_3$		47[c]
2		Pd(OAc)$_2$/3PPh$_3$		78
3		Pd(OAc)$_2$/3PPh$_3$		80
4		Pd(OAc)$_2$/3PPh$_3$		71
5		Pd(OAc)$_2$/dppf/PPh$_3$[d]		50
6		Pd(OAc)$_2$/3PPh$_3$		71
7		Pd(OAc)$_2$/3PPh$_3$		64

[a] See the experimental procedure in the text. [b] Isolated yields by column chromatography based on **1**. [c] The corresponding reaction with 6-bromo-4,4-di(methoxycarbonyl)hept-6-enal for the seven-membered cyclization failed owing to the intermolecular reaction or enolization of aldehyde. [d] dppf is 1,1′-bis(diphenylphosphino)ferrocene.

ation of carbonyl can be explained by the similar process for that of intermolecular allylboration which proceeds through a six-membered cyclic transition state **6** formed by coordination of boron atom to the carbonyl oxygen.[1]

The following procedure is representative. A dry flask was charged with Pd(OAc)$_2$ (0.03 mmol) and PPh$_3$ (0.09 mmol), and flushed with nitrogen. To the flask was added benzene (6 ml), **1** (1 mmol), and a solution of **2** in THF (1.5 mmol). After being stirred for 3 h at 70 °C, the reaction mixture was treated with water at room temp. The product was extracted with diethyl ether, washed with brine, dried (MgSO$_4$), and finally purified by chromatography over silica gel.

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Footnote

† ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.28 (t, 3 H, J 6.8 Hz), 1.35–1.76 (m, 11 H), 1.89–1.94 (m, 2 H), 2.01–2.11 (m, 1 H), 2.47–2.54 (m, 1 H), 4.10–4.24 (m, 2 H, J 6.8 Hz), 4.67 (broad s, 1 H), 5.00 (dd, 1 H, J 1.6 and 17.6 Hz), 5.07 (dd, 1 H, J 1.6 and 10.7 Hz), and 6.08 (ddd, 1 H, J 6.1, 10.7, and 17.6 Hz). The irradiation of allylic hydrogen at δ 2.50 enhanced the signals at 1.28 (OCH$_2$*Me*), 4.18 (OC*H*$_2$Me), 4.67 (OH), and vinylic three protons.

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