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A Convenient Synthesis of β,γ-Unsaturated Ketones *via* Allylation of *Z*-1-Halo-1-Alkenyl-1,3,2-Dioxaborolane

Herbert C. Brown* and Raman Soundararajan

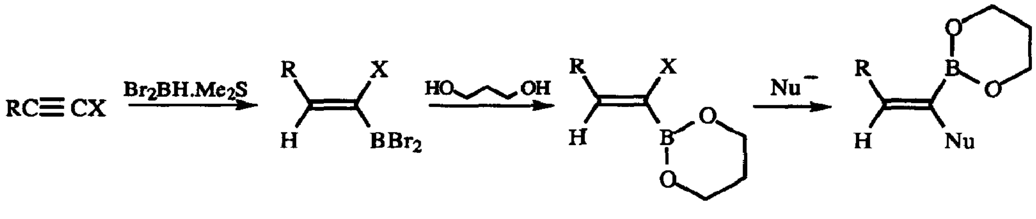
H.C. Brown and R.B.Wetherill Laboratories of Chemistry, Purdue University,
West Lafayette, Indiana 47907 U.S.A

Abstract: *A convenient, general synthesis of β,γ-unsaturated ketones via allylation of Z-1-halo-1-alkenyl-1,3,2-dioxaborolane has been developed. The reactivity under different conditions and the effect of an additive, HMPA, is elucidated. A representative procedure for the synthesis of 1-nonen-3-one is described.*

Synthesis of β,γ- unsaturated ketones poses difficulty due to the inherent lability of the double bond toward prototropic rearrangement. Many synthetic approaches produce isomeric mixtures of α,β- and β,γ-unsaturated compounds.[1-3] The C-C connectivity approach, such as acylation of olefins, is limited in scope.[3] Certain transition metal mediated syntheses have been partially successful, but they also suffer from poor regiospecificity.[4] Among other methods, direct oxidation of homoallylic alcohols produced via allylboration has been demonstrated to be successful for specific classes.[5] Claisen rearrangement of α-alkoxy ketone enolates or of the corresponding trimethylsilyl enol ethers provides β,γ-unsaturated ketones with good selectivity but the procedure is tedious.[6] In view of the synthetic importance of these ketones, it was desirable to have a general, convenient methodology for their synthesis especially from readily available starting materials.[7]

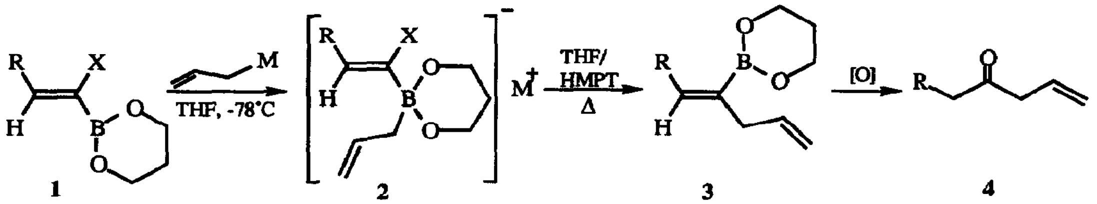
In the past, we had developed many applications utilizing organoboranes for carbon-carbon bond forming reactions.[8-10] In this regard, 1-halo-1-alkenylboronic esters, readily available *via* hydroboration of 1-halo-1-alkynes, are uniquely suited for providing meaningful and improved methodologies.[11-13] They undergo nucleophilic substitution quite readily with complete inversion of configuration at the vinylic center (Scheme I).[11] Earlier, we had prepared a series of stereodefined [*E*]- and [Z]- alkyl substituted alkenylboronates in good yields and in excellent stereochemical purities.[12] More recently, we have made a series of stereospecific 1,3-dienylboronic esters *via* nucleophilic displacement of 1-halo-1-alkenylboronate with stereodefined alkenyllithium reagents.[13]

As part of continuing investigations of the nucleophilic displacement reactions of 1-halo-1-alkenylboronates, we now report the reactions of these boronates with allylmagnesium chloride (Scheme II). The product, *E*-1-(2-propenyl)-1-alkenyl-1,3,2-dioxaborolane, formed in good yields, can be oxidized to β,γ-unsaturated ketones regioselectively, wherein the starting alkenylboronate serves as a masked acyl group equivalent.



Scheme I

It is well known that alkyl and alkenyl groups undergo facile rearrangement reactions with 1-halo-1-alkenylboronate displacing halide with ease.[11-13] However, initially the reaction of allylmagnesium chloride with 1-bromo-1-hexenylboronate in THF gave only moderate conversion (40-45%) even after 24 h at room temperature. The reaction, monitored using ^{11}B NMR spectroscopy (disappearance of the initially formed 'ate' complex at ≈ δ 0 ppm and the appearance of the boronate peak at δ 21 ppm), showed that even though the 'ate' complex **2** was formed as soon as the addition of allylmagnesium chloride was complete, the subsequent migration to **3** was sluggish. Higher reaction temperature did not enhance the rate of conversion appreciably, probably due to a stronger 'ate' complex. We envisaged that necessary solvation of the metal ion would enhance the rearrangement.[14] Indeed, addition of HMPA to the reaction mixture produced considerable enhancement of the rate of rearrangement. Essentially quantitative conversion to **3** was achieved in 6-8 hours at 45-50°C. Similar results were realized with TMEDA instead of HMPA. Oxidation with alkaline hydrogen peroxide produced the desired product, **4**.



Scheme II

As expected, changing the halogen from bromo to iodo also increases the rate of rearrangement. It is interesting to note that the rate and the yield is much higher for the iodo compound even in the absence of

HMPA. Again the use of allyllithium instead of allylmagnesium chloride provided high yields at room temperature in the presence of HMPA as a cosolvent.[15] The following table summarizes the results with representative 1-halo-1-alkenylboronates under various conditions.

Table. Reaction of Z-1-Halo-1-Alkenyl-1,3,2-Dioxaborolane (1) with Allylmetal Reagent in THF

no.	1		CH_2=CH-CH_2M	temp., °C	time, h	additive[b]	%yield[c]
	R	X	M[a]				
1	*n*-Bu	Br	MgCl	22	48	none	45-50
2	*n*-Bu	Br	MgCl	50	20	none	60
3	*n*-Bu	Br	MgCl	50	6	HMPA	95[d]
4	*n*-Bu	Br	MgCl	50	6	TMEDA	92
5	*n*-Bu	Br	Li[e]	22	4	HMPA	96
6	*n*-Pen	I	MgCl	22	20	none	82[d]
7	Chx	Br	MgCl	50	8	HMPA	72
8	Chx	I	MgCl	25	10	none	95
9	Cl $(CH_2)_3$	I	MgCl	25	6	none	90
10	*t*-Bu	Br	MgCl	50	24	HMPA	80

[a] 1.1 eq of the reagent was used. [b] HMPA or TMEDA used was 20-40% volume of THF. [c] Based on NMR data
[d] Isolated yields. [e] Prepared from the corresponding tri *n*-butyltin compound.

These boronates are readily converted to the β,γ-unsaturated ketones. A representative procedure for the synthesis of 1-nonen-3-one is as follows. 1-Bromo-1-hexenyl-1,3,2-dioxaborolane[11] (2.47g; 10 mmol) was dissolved in anhydrous THF (10 mL) and cooled to -78°C under a stream of argon. Allylmagnesium chloride (11 mmol; 5.5 mL of 2M solution in THF) was added slowly to this solution while stirring vigorously. The cooling bath was removed after 5 min and the contents allowed to warm to room temperature. Anhydrous HMPA (4 mL) was then added and the mixture heated to 45-50°C. The reaction was monitored using ^{11}B NMR spectroscopy by the disappearance of the 'ate' complex at ~ δ 0 ppm and the appearance of the product at δ 21 ppm. At the end of the reaction, the contents were cooled and diluted with *n*-pentane (20 mL), washed with water (2x25 mL), dried over anhy. $MgSO_4$, and the solvents removed under vacuum. The crude product was oxidized using NaOAc / H_2O_2 according to the published procedure.[8a] The product 1-nonen-3-one[5a] (4, R=*n*-Bu) (1.12g, 77%; b.p.65-66°C / 15 mm Hg) was promptly distilled to avoid possible isomerization.[16]

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16 It is important to distill the ketone from basic impurities as soon as possible to avoid slow isomerization to the α,β- unsaturated isomer.

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