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A highly diastereoselective synthesis of (*E*)-*B*-2-(1-cyclopropyl-1-alkenyl)-1,3,2-dioxaborinanes. Isolation and oxidation to alkyl cyclopropyl ketones

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Abstract—A convenient, novel synthesis of alkyl cyclopropyl ketones based on *Z*-1-bromo-1-alkenylboronate esters is developed. α-Bromo-(*Z*)-1-alkenylboronate esters readily available from literature procedures smoothly undergo a reaction with cyclopropylmagnesium bromide in tetrahydrofuran to provide the corresponding 'ate' complexes. These 'ate' complexes undergo intramolecular nucleophilic substitution reactions to provide the corresponding (*E*)-1-alkenylboronate esters containing cylcopropyl moiety for the first time in good isolated yields (68–82%). The carbon skeleton present in these intermediates is confirmed by oxidation with hydrogen peroxide and sodium acetate to afford the corresponding alkyl cyclopropyl ketones in good yields (72–85%).

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1. Introduction

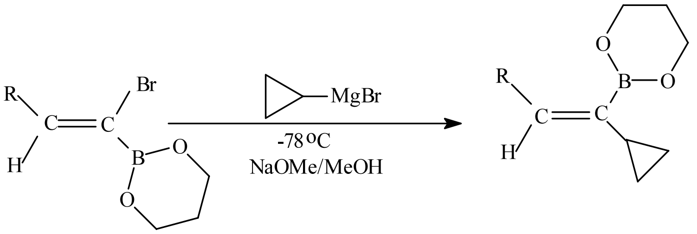
The cyclopropyl ketones are important intermediates[1] in organic synthesis. There are several reports[2,3] for their syntheses in literature. Recently, Deng and co-workers have reported[4] a stereocontrolled synthesis of 1,2-*trans* cyclopropyl ketones via Suzuki-type coupling of acid chlorides with cycloproprопylboronic acids. They are potential prochiral ketones for asymmetric reduction reactions. In view of the synthetic importance of alkyl cyclopropyl ketones, it is desirable to have a general, convenient methodology to their synthesis especially from readily available organoborane reagents.

In a previous study, a stereoselective preparation of the (*Z*)-1-bromo-1-alkenylboronate esters via the hydroboration of 1-bromo-1-alkynes followed by treatment with 1,3-propane diol has been reported.[5] It should be noted that these α-halo-(*Z*)-1-alkyenylboronate esters are known to undergo intramolecular nucleophilic substitution reactions[6–9] with nucleophiles such as hydrides,[10] Grignard reagents,[11] organolithium reagents,[11] allylmagnesium bromide[12] and trimethylsilylmethyllithium.[13]

2. Results and discussion

In this report, we reacted 1-bromo-(*Z*)-1-hexenylboronate esters with a nucleophilic reagent such as cyclopropylmagnesium bromide in ether in the presence of an additive such as sodium methoxide in methanol (Eq. (1)).

After aqueous work-up followed by esterification with 1,3-propane diol in *n*-pentane, the isolated (*E*)-1-alkenylboronate esters containing cylcopropyl moiety were subjected to oxidation with hydrogen peroxide and sodium acetate (Eq. (2)). Consequently, we describe a facile general synthesis of alkyl cyclopropyl ketones based on versatile intermediates such as α-bromo-(*Z*)-1-alkenylboronate esters.



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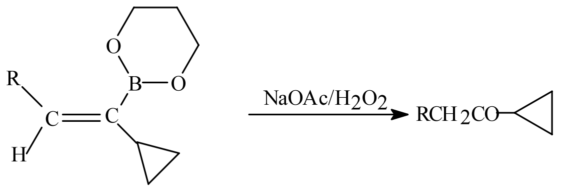

(2)

The required starting materials such as 1-bromo-1-alkynes and α-bromo-(Z)-1-alkenylboronate esters are prepared using literature procedures.[5] In a typical experiment, α-bromo-(Z)-1-hexenyl boronate ester in ether was reacted with a solution of cyclopropylmagnesium bromide in tetrahydrofuran at −78°C under an inert atmosphere and the reaction mixture was stirred at −78°C for 2 h. Two equivalents of sodium methoxide in methanol was added at −78°C followed by stirring overnight at room temperature. After aqueous workup, the resulting boronic acid was esterified with 1,3-propane diol at room temperature. The solvents were then pumped off and the resulting product was isolated by distillation to provide the corresponding (E)-B-2-(1-cyclopropyl-1-hexenyl-1,3,2-dioxaborinane (entry 1 in Table 1) in 82% isolated yield. It was then subjected to oxidation using hydrogen peroxide and sodium acetate in tetrahydrofuran at room temperature for 4 h. After workup, the reaction provided n-pentyl cylcopropyl ketone (entry 1 in Table 2) in 80% isolated yield. Using the above procedure, the representative (E)-B-2-(1-cyclopropyl-1-alkenyl)-1,3,2-dioxaborinanes were prepared (Table 1) and representative alkyl cylcopropyl ketones were prepared (see Table 2).

Presumably, the starting α-bromo-(Z)-1-alkenylboronate ester could form an 'ate' complex as a result of a reaction with cyclopropylmagnesium bromide. This would further undergo an anionotropic rearrangement involving the migration of the cyclopropyl group from boron to the adjacent alkenyl carbon with inversion of configuration to provide (E)-trisubstituted boron intermediate containing cyclopropyl moiety, the oxidation of which would provide alkyl cyclopropyl ketones. The mechanism of the reaction of α-bromo-(Z)-1-alkenylboronate ester with cyclopropylmagnesium bromide is shown below (Eq. (3)).

Table 1. Diastereoselective synthesis of (E)-B-2-(1-cyclopropyl-1-alkenyl)-1,3,2-dioxaborinanes (Eq. (1))

Entry	R =	Isolated yield[a,b] (%)
1	n-C_4H_9	82
2	n-C_5H_{11}	75
3	n-C_6H_{13}	78
4	n-$Cl(CH_2)_3$	72
5	-$C(CH_3)_3$	68
6	-$CH_2CH_2CH(CH_3)_2$	80

[a] All of the reactions were carried out on a 10 mmol scale. The yields were based on the corresponding α-bromo-(Z)-1-alkenylboronate esters.

[b] All of the compounds were purified by vacuum distillation. The stereochemistry[14,15] was established by ^{1}H and ^{13}C spectral data.

Table 2. Synthesis of alkyl cyclopropyl ketones via organoboranes (Eq. (2))

Entry	R =	Isolated yield (%)[a,b]
1	n-C_4H_9	80
2	n-C_5H_{11}	82
3	n-C_6H_{13}	85
4	n-$Cl(CH_2)_3$	72
5	-$C(CH_3)_3$	73
6	-$CH_2CH_2CH(CH_3)_2$	74

[a] All of the reactions were carried out on a 10 mmol scale. The yields were based on the corresponding α-bromo-(Z)-1-alkenylboronate esters.

[b] All of the compounds were isolated by column chromatography over alumina and were characterized by IR and NMR spectral data.

3. Conclusions

In summation, we have developed a novel synthetic route for the preparation of alkyl cyclopropyl ketones based on the reactions of cyclopropylmagnesium bromide with α-bromo-(Z)-1-alkenylboronate esters followed by oxidation. We have successfully isolated the potential organoborane intermediate precursors to alkyl cyclopropyl ketones and confirmed their structures for the first time by NMR spectral data. The representative synthetic applications of these (E)-trisubstituted organoborane intermediates containing cyclopropyl moiety are also currently underway.

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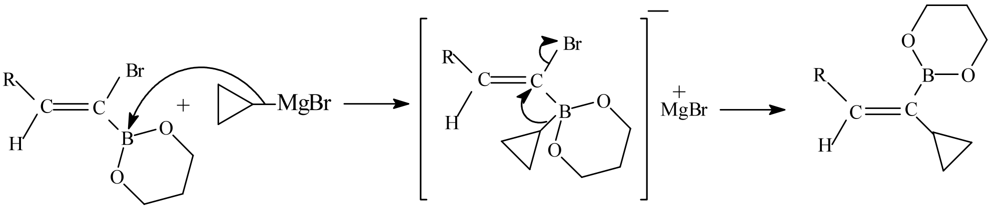

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