Synthesis of 4-substituted homoallylic alcohols *via* a one-pot tandem Lewis-acid catalyzed crotylboration-[3,3]-sigmatropic rearrangement

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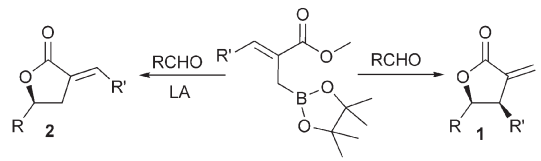
Crotylboration of aldehydes with *E*- or *Z*-crotylboronates in the presence of catalytic amounts of indium triflate provides the corresponding 4-substituted homoallylic alcohols.

Crotylboration using various allylboronates leads to the formation of 2-substituted homoallylic alcohols, which are important units for the synthesis of various biologically active complex natural products.[1] This reaction has been well studied for the ready access of this class of compounds.[2] Herein we report a controlled *in situ* conversion of aldehydes to 4-substituted homoallylic alcohols *via* Lewis acid-catalyzed crotylboration.

Recently, we reported the room and high temperature allylboration of aldehydes with functionalized allylboronates for the preparation of α-methylene-γ-butyrolactones **1** [eqn. (1)].[3] To accelerate the reactions at lower temperatures, we were examining the effect of Lewis acid catalysis.[4] During this process, we observed the formation of α-alkylidine-γ-butyrolactones **2** as the major products [eqn. (1)].[5]



(1)

This unexpected reaction prompted us to examine the Lewis acid-catalyzed crotylboration of aldehydes with crotylboronates.[6] We examined $In(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Zn(OTf)_2$, $ZnCl_2$, $SnCl_4$, and $MgCl_2$ as possible Lewis acids and found that $In(OTf)_3$ gave the best results. Our initial investigation revealed that crotylboration of benzaldehyde at −78 °C with both (*Z*)- and (*E*)-crotylboronate (**3a** and **3b**) in the presence of 10% $In(OTf)_3$ provided the expected 2-substituted homoallylic alcohols **4a** and **4b** respectively. However, when the same reaction was carried out at room temperature, the corresponding 4-substituted homoallylic alcohols, **5a** and **5b** respectively, were obtained with very high regioselectivity. Conversion of 2-substituted homoallylic alcohols to the corresponding 4-substituted derivatives *via* a [3,3]-sigmatropic rearrangement was, recently, independently reported by Nokami[7] and Loh[8] and their co-workers.

When the reaction was carried out at room temperature with 0.8 equiv. of the aldehyde, we obtained a 4:1 ratio of **4a** and **5a**, with **4a** as the major product. Thus, we have demonstrated that, at will, we can obtain 2-substituted or 4-substituted homoallylic alcohols *via* crotylboration either by changing the reaction temperature or by changing the equivalents of the aldehyde at room temperature (Scheme 1).

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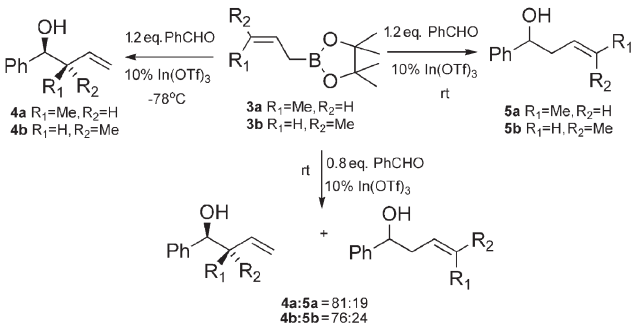
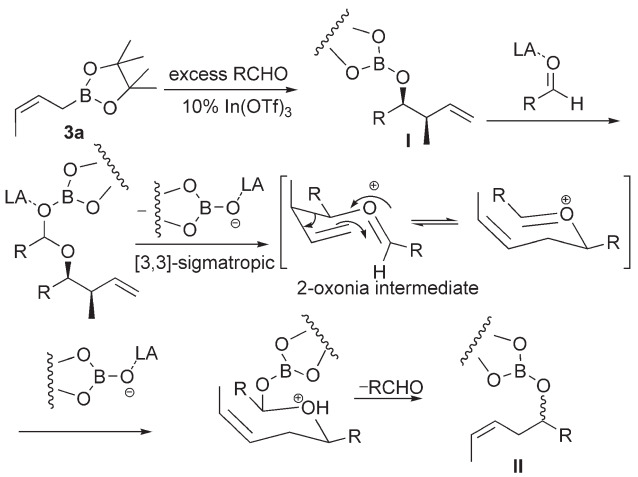
We accounted for the formation of the rearranged borate intermediate **II** *via* a similar sigmatropic rearrangement of the borate intermediate **I** derived from initial crotylboration. A slight excess of aldehyde is necessary for this conversion as elucidated in Scheme 2. Indeed, crotylborations are typically carried out with 1.2 equiv. of aldehyde.

After careful investigation of the effect of temperature and equivalents of aldehyde on Lewis acid-catalyzed crotylboration, we extended our study to a variety of aldehydes. Crotylboration of hexanaldehyde with (*E*)-crotylboronate **3b** was complete within 45 min, with the corresponding α-adduct **6b** being formed predominantly. The stereochemistry of the reagent was exclusively transferred to the product. [(*E*)-reagent to (*E*)-adduct] (Table 1, entry 6). A similar result was obtained with (*Z*)-crotylboronate (Table 1, entry 2). Isobutyraldehyde provided the rearranged products **7a** and **7b**, albeit in poor yields, with (*Z*) and

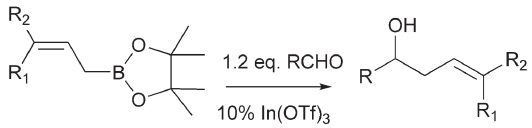


Scheme 1



Scheme 2

Table 1 Preparation of 4-substituted homoallylic alcohols



3a, R_1=Me, R_2=H
3b, R_1=H, R_2=Me

5a-8a, R_1=Me, R_2=H
5b-8b, R_1=H, R_2=Me

Entry	Reagent	R	Time (min)	Product	Yield (%)	*E*:*Z*[9]
1	**3a**	Ph	15	**5a**	87	<1:>99
2	**3a**	*n*-Pent	25	**6a**	65	<1:>99
3	**3a**	*i*-Pr	150	**7a**	30	<1:>99
4	**3a**	Cy	210	**8a**	65	<1:>99
5	**3b**	Ph	15	**5b**	90	>99:<1
6	**3b**	*n*-Pent	45	**6b**	70	>99:<1
7	**3b**	*i*-Pr	120	**7b**	30	>99:<1
8	**3b**	Cy	180	**8b**	96	>99:<1

(*E*)-crotylboronate respectively (Table 1, entries 3 and 7). We are currently examining the low yields. Crotylboration of cyclohexane carboxaldehyde with (*E*)-crotylboronate **3b** provided the α-adduct **8b** in 96% yield and >99% *E*-selectivity.[9] (Table 1, entry 8). The corresponding *Z*-product **8a** was obtained in 65% yield with high selectivity.

In conclusion, we have described the first example of an *in situ* $In(OTf)_3$-catalyzed crotylboration of aldehydes for the preparation of 4-substituted homoallylic alcohols *via* a tandem crotylboration-[3,3]-sigmatropic rearrangement in the presence of a slight excess of aldehydes. The chiral variant of this reaction is under investigation.

A typical procedure for the crotylboration-rearrangement of aldehydes with **3a** or **3b** is as follows. Preparation of (*Z*)-crotylboronate (**3a**): KO^{t}Bu (1 mmol) was taken up in 2 mL anhydrous THF and cooled to −78 °C. *cis*-2-Butene (1.5 mmol) was condensed in a −78 °C bath and transferred to the reaction mixture. *n*-BuLi (2.5 M in hexane, 1 mmol) was then added dropwise so that the temperature was maintained below −50 °C. After completion of the addition, the cooling bath was removed and the reaction mixture was stirred at −50 °C for 30 min. The solution was then recooled to −78 °C. Triisopropylborate (1 mmol) was then added dropwise to the (*Z*)-crotylpotassium solution and stirred for 30 min at −78 °C. The solution was rapidly poured into separating funnel containing 10 mL of 1N HCl saturated with NaCl. A solution of pinacol (1.1 mmol) in 5 mL THF was added directly to the separating funnel. The two phases were separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and was concentrated under vacuum to obtain the (*Z*)-crotylboronate (**3a**) in >99% isomeric purity.

(*E*)-Crotylboronate (**3b**) was obtained in >99% isomeric purity from *trans*-2-butene by using an identical procedure as above.

Allylboration at −78 °C: **3a** or **3b** (1 mmol) was dissolved in toluene. $In(OTf)_3$ (0.12 mmol) was added to the above solution and the solution was cooled to −78 °C. Aldehyde (1.2 mmol) was added and the reaction mixture was stirred at −78 °C until the reaction was complete (monitored by ^{11}B NMR: crotylboronate peak at δ 33 ppm disappeared and a peak at δ 22 ppm was observed). The solution was then washed with sat. NH_4Cl (2 mL) and extracted with ether (3 × 5 mL). The combined organic layer was then washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was then purified by column chromatography (silica gel, hexanes:ethyl acetate: 95:5) to obtain **4a** or **4b**.

Allylboration at room temperature: **3a** or **3b** (1 mmol) was dissolved in toluene. $In(OTf)_3$ (0.12 mmol) was added to the above solution at room temperature followed by the addition of aldehyde (1.2 mmol) and the reaction mixture was stirred at room temperature until the reaction was complete (monitored by ^{11}B NMR: crotylboronate peak at δ 33 ppm disappeared and a peak at δ 22 ppm was observed). The solution was then washed with sat. NH_4Cl (2 mL) and extracted with ether (3 × 5 mL). The combined organic layer was then washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was then purified by column chromatography (silica gel, hexanes:ethyl acetate: 95:5) to obtain **5a–8a** or **5b–8b**.

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9 Only one isomer was detected in the ^1H NMR spectrum of the crude sample.