

Preparation of Bifunctional Allylboron Reagent and Application to Aldehyde Allylboration

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Supporting Information

ABSTRACT: Synthesis of a bifunctional allylboron reagent via Ni-catalyzed borylation of allylic acetate is reported. Subsequent allylation of aldehydes gave homoallylic alcohols in good yields. The allylsilane moiety in the alcohol product serves as a useful handle for subsequent transformations.

KEYWORDS: bifunctional allylation reagent, Ni-catalyzed allylic borylation, allylboronate, homoallylic alcohol

Allylic organometallics (I, Scheme 1) are useful bifunctional allylation reagents in organic synthesis.^{1,2} The

Scheme 1. Reaction of Aldehyde with Bifunctional Allylation Reagent I



addition of reagent I to carbonyl compounds, aldehyde for instance, produces homoallylic alcohols and simultaneously unveils an allylmetal unit that is poised for a second allyl addition event. However, complications may arise when the chemical reactivities of two allylmetal units in reagent I are similar to each other, and as a result, a mixture of products (e.g., II and III) can be generated. Therefore, when designing such reagents, two allylmetal units often need to have orthogonal reactivities to eliminate such complications.

Toward this end, several bifunctional allylation reagents I, which meet such a requirement, have been developed. For example, the allylstannane unit in reagent B [2-(trimethylsilylmethyl) allyltri-*n*-butylstannane] selectively reacted with aldehydes to give homoallylic alcohols 3 in the presence of a Lewis acid (eq 1, Scheme 2).^{3,4} By taking advantage of the different reactivities of allylboron and allylsilane toward carbonyl addition, Williams and co-workers developed a bifunctional allylation reagent C from organotin reagent B.⁵ The reaction of C with aldehydes produced the same alcohol products 3 (eq 2, Scheme 2). More recently, 2-(trimethylsilylmethyl) allylborane reagent E was synthesized from the allylselenium precursor **D** by the Kadota group (eq 3, Scheme 2).⁶ Addition of E to aldehydes also afforded alcohols 3. However, these important achievements are not without any drawback. Organoboron reagent E is known to be moisture and oxygen sensitive, while preparation of reagent C requires

Scheme 2. Approaches to Homoallylic Alcohol 3 via Bifunctional Allylation Reagents

Previous work:



organotin reagent **B**. The development of a nontoxic, air- and moisture-stable reagent to address these disadvantages is therefore valuable.

With our continuing interest in allylation chemistry, we set a goal to develop a reagent to solve this problem. We chose allylboronate 2 (Scheme 2) as the targeted reagent because it is not toxic and, moreover, should be stable to air and moisture. It is quite surprising that such a simple allylboronate reagent has not been synthesized previously. We report herein the preparation of this reagent via Ni-catalyzed borylation of the commercially available allylic acetate 1 (eq 4, Scheme 2). Reagent 2 readily reacts with aldehyde to give homoallylic alcohol 3 that has an allylic silane moiety as a useful handle for subsequent transformations.

We began our studies by developing the reaction conditions for borylation of allylic acetate **1**. The initial experiments were conducted with CuCl as the catalyst for allylic borylation.⁷ While the reaction did not occur in the absence of a ligand, ¹H

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NMR spectroscopy indicated that allylic acetate 1 was fully converted to reagent 2 with 5 mol % of Xantphos or dppbz as the ligand in 24 h at ambient temperature. In addition, the combination of Ni(cod)₂ and PPh₃ is also an effective catalytic system to convert allylic acetate 1 to 2.8 However, although reagent 2 is not moisture and oxygen sensitive, it is not stable enough toward flash column chromatography purification. Therefore, subsequent experiments were conducted to probe whether the aldehyde allylation step can be carried out in a one-pot manner. After full consumption of allylic acetate 1, benzaldehyde was added to the same reaction vessel. Gratifyingly, the allylation was complete in 30 min at ambient temperature, and homoallylic alcohol 3a was generated from the reaction. The reaction catalyzed by CuCl and Xantphos gave product 3a in 83% yield. In the case of CuCl and dppbz, 3a was isolated in a much lower yield. The reaction under the Ni system provided homoallylic alcohol 3a in 73% yield (Table 1). In the absence of $B_2 pin_2$, however, the Ni-catalyzed

Table 1. Evaluation of the Reaction Conditions for Allylic Borylation and Aldehyde Allylation Reaction Sequence^a

	$\frac{e_3}{DAc} \xrightarrow{\text{catalyst}}{B_2 \text{pin}_2}$	SiMe ₃ BPin 2	$\left[\begin{array}{c} PhCHO \\ \hline rt \end{array} \right]$	Ph 3a
entry	catalyst	ligand	base	yield (3a) (%) ^b
1	CuCl	no ligand	KOt-Bu	NR
2	CuCl	Xantphos	KOt-Bu	83
3	CuCl	dppbz	KOt-Bu	17
4 ^{<i>c</i>}	$Ni(cod)_2$	PPh ₃	no base	73

"Reaction conditions: allylic acetate 1 (0.15 mmol, 1.5 equiv), CuCl (10 mol %), ligand (10 mol %), KOt-Bu (0.18 mmol, 1.8 equiv), B_2pin_2 (0.18 mmol, 1.8 equiv), THF (0.3 mL), rt, 24 h; then benzaldehyde (0.1 mmol, 1.0 equiv), rt, 2 h. ^bYields of isolated products are listed. ^cAllylic acetate 1 (0.15 mmol, 1.5 equiv), Ni(cod)₂ (5 mol %), PPh₃ (5 mol %), B_2pin_2 (0.18 mmol, 1.8 equiv), toluene (0.3 mL), 60 °C, 2 h; then benzaldehyde (0.1 mmol, 1.0 equiv), rt.

reaction did not produce any **3a**. The Ni catalyst can be removed by simply filtering the crude reaction mixture through a short pad of Celite after completion of the reaction. The obtained stock solution of reagent **2** can be stored at -20 °C over 2 weeks with only minimal decomposition (<10%; please see Supporting Information for details). By contrast, it was not feasible to obtain a stock solution of reagent **2** in the cases of Cu-catalyzed reactions. Therefore, we chose the catalytic system of Ni(cod)₂ and PPh₃ to explore the scope of aldehyde for this reaction.

The reaction conditions developed for the synthesis of **3a** were then applied to reactions with a variety of aldehydes, and the results are summarized in Scheme 3. Allylation of aromatic aldehydes bearing an electron-donating or electron-with-drawing substituent at the *para*-position of the arene provided products **3b**-**d** in 77–92% yields. Halogen-substituted aromatic aldehydes reacted to afford alcohols **3e**-**h** in 79–98% yields. Similar results were obtained with α,β -unsaturated aldehydes, and alcohols **3i**-**k** were formed in 67–82% yields. Reactions with heteroaromatic aldehydes occurred smoothly to furnish products **3l**-**n** in 67–95% yields. Finally, aliphatic aldehydes are also suitable reaction partners, and alcohols **3o**-**r** were obtained in 67–97% yields. It should be noted that the allylsilane moiety in homoallylic alcohols **3** is sensitive to acidic

Scheme 3. Synthesis of Homoallylic Alcohols 3 via Allylic Borylation and Aldehyde Allylation a,b



^aAllylic acetate 1 (0.15 mmol, 1.5 equiv), $Ni(cod)_2$ (5 mol %), PPh_3 (5 mol %), B_2pin_2 (0.18 mmol, 1.8 equiv), toluene (0.3 mL), 60 °C, 2 h; then aldehyde (0.1 mmol, 1.0 equiv), rt. ^bYields of isolated products are listed.

conditions. For instance, homoallylic alcohols 3 were slowly decomposed in deuterated chloroform.⁹ However, they are perfectly stable in d^6 -acteone or d^8 -toluene.

*cis-2,6-Disubstituted tetrahydropyran is a common scaffold in numerous natural products (Figure 1).*¹⁰ As many strategies



Figure 1. Selected *cis*-2,6-disubstituted tetrahydropyran-containing natural products.

have been developed to construct such a structural entity, homoallylic alcohols **3** can also be utilized to synthesize tetrahydropyrans.³ As shown in Scheme 4, in the presence of

Scheme 4. Stereoselective Synthesis of *cis*-2,6-Disubstituted Tetrahydropyran from Homoallylic Alcohol 3



TMSOTf, reactions of alcohol **3p** with a few representative aldehydes gave *cis*-2,6-disubstituted tetrahydropyran products **4a**-**c** in 70–96% yields with >20:1 diastereoselectivities (determined by NOE studies). In addition, 4-hydroxyl-tetrahydropyran **5** was obtained in 98% yield via a one-pot ozonolysis and reduction reaction sequence from **4a**. The stereochemistry of the newly formed hydroxyl group was assigned by NOE studies.

In summary, we developed a Ni-catalyzed borylation of allylic acetate to access bifunctional allylation reagent 2. Reagent 2 readily reacted with a variety of aldehydes to give homoallylic alcohols 3 in good yields. The allylsilane unit embedded in product 3 serves as a useful handle for additional functional group transformations, as illustrated by diastereoselective synthesis of *cis*-2,6-disubstituted tetrahydropyrans.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00168.

Experimental procedures, spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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