

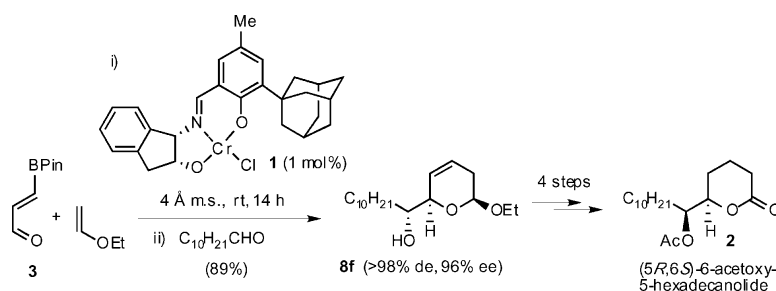
Communication

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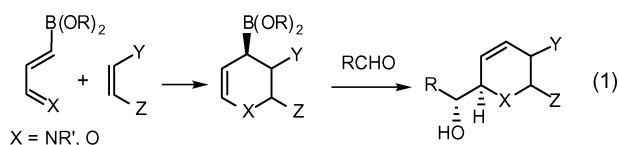
3-Boronoacrolein as an Exceptional Heterodiene in the Highly Enantio- and Diastereoselective Cr(III)-Catalyzed Three-Component [4+2]/Allylboration

Xuri Gao and Dennis G. Hall*

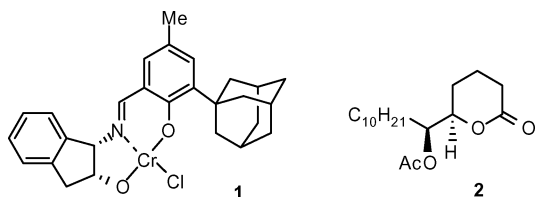
Department of Chemistry, University of Alberta, Edmonton, AB, T6G 2G2, Canada

Received May 27, 2003; E-mail: dennis.hall@ualberta.ca

Pyran and dihydropyran units are ubiquitous components that present a wide variety of substitution patterns in several classes of biologically active natural products. Consequently, there is significant interest in the development of new synthetic methodologies to access polysubstituted pyran derivatives in optically pure form.¹ To this end, multicomponent reaction strategies are particularly attractive because of their operational simplicity and high degree of convergence.² Our laboratory reported the first examples of a three-component hetero[4+2]/allylboration strategy to construct α -hydroxyalkylated heterocycles (eq 1).³ While optically pure polysubstituted piperidines can be synthesized from chiral 4-borono-1-azabutadienes,³ the corresponding process to construct pyran units from 3-boronoacrolein is devoid of an asymmetric variant.⁴



We envisioned that 3-boronoacrolein esters could be viable substrates in Jacobsen's enantioselective inverse electron demand hetero[4+2] reaction with enol ethers (X = O, Z = OEt; eq 1), catalyzed by the tridentate (Schiff base)chromium complex **1**.⁵ The intermediate cyclic allylboronate could be further reacted with an added aldehyde in a sequential fashion to provide the α -hydroxyalkyl dihydropyran as the final product. The ability to perform this three-component sequence in an operationally simple one-pot reaction, with either a thermal or a Lewis-acid-catalyzed allylboration,⁶ would add significant value to this strategy. Herein, we report the optimization of the first catalytic enantio- and diastereoselective hetero[4+2]/allylboration reaction to provide efficient access to α -hydroxyalkyl pyran derivatives. This one-pot three-component reaction was successfully applied to a concise total synthesis of (5*R*,6*S*)-6-acetoxy-5-hexadecanolide (**2**), the oviposition attractant pheromone⁷ of the female *Culex* mosquito capable of transmitting the West Nile virus.⁸



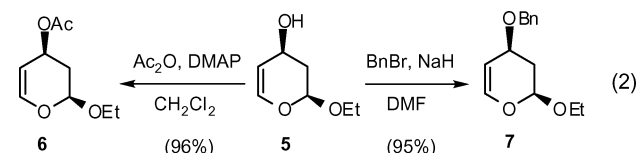
Initial optimization studies focused on optimizing conversion and enantioselectivity in the formation of cyclic allylboronate **4** by hetero-Diels–Alder reaction between ethyl vinyl ether and 3-boronoacrolein pinacolate (**3**) catalyzed by **1** (Table 1). The enantiomeric excess was measured on the corresponding secondary alcohol product **5** following oxidation/hydrolysis of the boronate substituent with retention of stereochemistry.⁹

Table 1. Optimization of the Hetero[4+2] Reaction between **3** and Ethyl Vinyl Ether Catalyzed by **1**^a

entry	catalyst loading ^b (mol %)	additive	conversion ^c (%)	ee ^d (%)
1 ^e	5	BaO	100	<50
2	5	BaO	100	95
3	5	4 Å m.s.	100	96
4	1	4 Å m.s.	100	96
5	0.5	4 Å m.s.	100	96
6	0.3	BaO	100	96

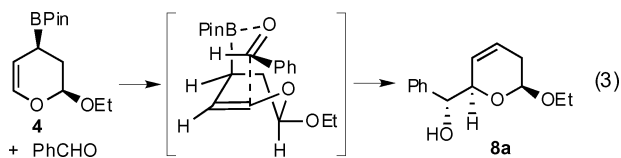
^a Pin = pinacolate. Conditions: 2 mmol (0.36 g) of distilled **3**, 1 M in vinyl ethyl ether (1.9 mL), room temperature, 14 h. ^b Relative to **3**. ^c Measured by integration of representative signals by ¹H NMR. ^d Measured by chiral HPLC (Chiralpak AD-RH column). ^e With nondistilled **3**.

At the outset, we realized that the purity of the key substrate 3-boronoacrolein pinacolate (**3**) is crucial. When using heterodiene **3** prepared in two steps from 3,3-diethoxy-1-propyne with our recently described distillation-free procedure,³ only a low ee could be obtained under the standard conditions⁵ using 5 mol % of catalyst **1** and BaO as the dehydrating agent for 14 h in neat ethyl vinyl ether (entry 1). Although the ¹H NMR spectrum of substrate **3** purified by distillation showed no noticeable difference from that of a sample obtained as before,³ the enantioselectivity was drastically improved (entry 2). The ee was equally high with molecular sieves instead of BaO as the dehydrating agent (entry 3). Our next goal was to reduce the catalyst loading (entries 4–6), and we were glad to observe that both conversion and ee remained very high with as low as 0.3 mol % of **1**.¹⁰ In comparison with the loading values of 5–10 mol % previously reported for a wide range of α,β -unsaturated aldehydes,⁵ this result suggests that 3-boronoacrolein pinacolate (**3**) is a particularly favorable heterodiene in this reaction. In fact, **3** serves as a valuable surrogate of 3-acyloxylacroleins, which were reported to afford the synthetically useful 4-hydroxy dihydropyran derivative in a lower selectivity (89% ee).⁵ Here, intermediate **5** was isolated in 81% yield and 96% ee from the hetero[4+2]/oxidation reaction of **3**. Routine transformations of the hydroxyl group of **5** led to other intermediates useful in allylic substitution chemistry (eq 2).



Following optimization of the hetero-Diels–Alder reaction, the second step in the three-component sequence, the allylboration, was

optimized using benzaldehyde (eq 3). To this end, hetero-Diels–Alder adduct **4** was isolated and purified using a short column of silica gel. The absence of allylboration product between **3** and **4** implies that the Cr(III)-catalyzed hetero[4+2] cycloaddition is significantly faster than aldehyde allylboration with intermediate **4**.



Allylboration reactions are usually carried out in noncoordinating solvents such as dichloromethane and toluene. To our surprise, we found that the reactivity of allylboronate **4** was not attenuated when using ethyl vinyl ether as solvent.¹¹ The addition occurs readily at a relatively low temperature (40 °C) and affords α -hydroxybenzyl dihydropyran **8a** as a single diastereomer consistent with the usual Zimmerman–Traxler transition structure (eq 3).^{3,4} Moreover, we found that it was not necessary to purify intermediate **4** and eliminate residual catalyst **1** when used only in a 1 mol % loading.¹² This way, the hetero[4+2]/allylboration sequence can be carried out in a one-pot procedure from **3** by simple addition of the aldehyde after completion of the cycloaddition step. As detailed in Table 2, suitable aldehyde substrates include aromatic aldehydes with different electronic characteristics, and aliphatic aldehydes including functionalized ones such as TBDMSOCH₂CHO (entry 5). All of these different aldehydes afforded dihydropyran products **8a–8h** in high yields. Reactions with α,β -unsaturated aldehydes required a change of solvent to dichloromethane to avoid a competing hetero[4+2] reaction with ethyl vinyl ether (entries 7–8).

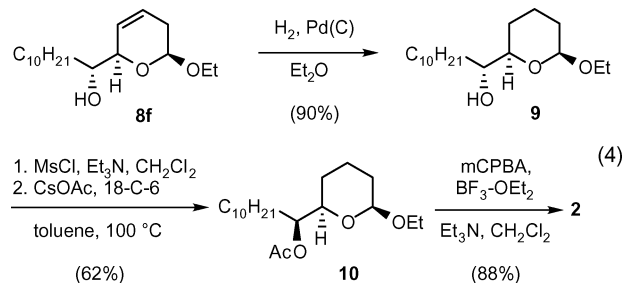
Table 2. Substrate Scope for the Catalytic Enantioselective Three-Component Hetero[4+2]/Allylboration Reaction^a

entry	aldehyde (R)	temp (°C)	time (h)	product ^b	yield ^c (%)
1	C ₆ H ₅	40	24	8a	82
2	4-NO ₂ -C ₆ H ₄	25	24	8b	92
3	4-MeO-C ₆ H ₄	45	24	8c	81
4	(CH ₃) ₂ CHCH ₂	45	24	8d	81
5	TBSOCH ₂	45	24	8e	82
6	C ₁₀ H ₂₁	45	24	8f	89
7 ^d	(E)-4-NO ₂ -C ₆ H ₄ CH=CH	40	24	8g	81
8 ^d	(E)-CH ₃ CH=(CH ₃)C	45	48	8h	61

^a Pin = pinacolate. Conditions: 2 mmol (0.36 g) of distilled **3**, 1 M in vinyl ethyl ether (1.9 mL), with 1 mol % of catalyst **1**, room temperature, 14 h, followed by the addition of 2.0 equiv of aldehyde and reaction at the indicated temperature and time. ^b Diastereomerically pure. Retention of the absolute stereochemistry in the allylboration of **4** is assumed on the basis of **8f** and its transformation onto enantiopure **2** (eq 4), which possesses the expected optical rotation value (see Supporting Information). ^c Unoptimized yields of products isolated after flash chromatography. ^d Ethyl vinyl ether was evaporated after step i and replaced with dichloromethane.

Undecanal (entry 6) is the aldehyde substrate required to establish the α -hydroxyalkyl side chain of (5*R*,6*S*)-6-acetoxy-5-hexadecanolid (2).¹³ This reaction was even carried out in gram scale (7 mmol of **3**), and the resulting dihydropyran **8f** was hydrogenated to

provide pyran intermediate **9** (eq 4). Acetylation of the secondary alcohol by inversion of configuration afforded **10**,¹³ and oxidation of the acetal¹⁴ led to the desired mosquito pheromone **2** after only seven steps from commercial 3,3-diethoxy-1-propyne. The presence of the C4–C5 unsaturation confers remarkable synthetic versatility to dihydropyrans **8**. For example, appropriate oxidation of the double bond would lead to carbohydrate derivatives and other highly oxygenated pyran-containing natural products.



This Communication described the first catalytic enantioselective hetero[4+2]/allylboration reaction. From the key substrate 3-boronoacrolein pinacolate, this one-pot, three-component reaction provides α -hydroxyalkyl dihydropyrans with very high enantio- and diastereoselectivity. Further extensions and applications of this powerful, practical process in the synthesis of complex natural products are underway.

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Supporting Information Available: Experimental procedures, characterization data (NMR, MS), and spectral reproductions for compounds **4–7**, **8a–8h**, **9**, **10**, and synthetic **2** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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