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α-Hydroxyalkyl Heterocycles via Chiral Allylic Boronates: Pd-Catalyzed Borylation Leading to a Formal Enantioselective Isomerization of Allylic Ether and Amine

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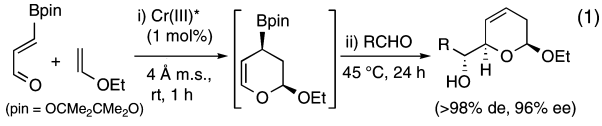
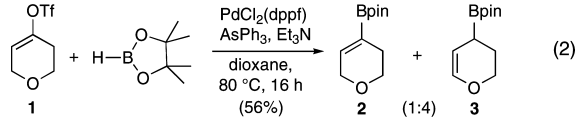
Several natural products and synthetic drugs are made of oxygen or nitrogen containing rings flanked by a hydroxyalkyl substituent next to the heteroatom. Notable examples include higher order sugars (e.g., β-KDO, a key component of the lipopolysaccharide cell wall of Gram-negative bacteria), numerous piperidine alkaloids, marine oligopyrans, and the antihypertension drug Nebivolol.[1] A powerful and highly stereoselective approach to these important heterocycles exploits the allylboration of aldehydes with chiral cyclic allylic boronates.[2] Despite its many attributes, this strategy is limited by a dearth of enantiocontrolled preparative methods for the required allylic boronates. One method, reported by our group, exploits a catalytic enantioselective hetero [4+2] cycloaddition approach to a pyranyl allylic boronate, which can react with high diastereoselectivity with aldehydes to provide the desired α-hydroxyalkyl dihydropyrans (eq 1).[3]



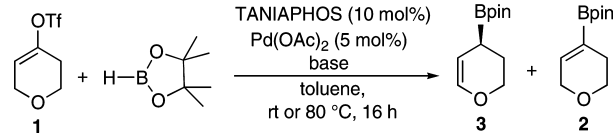
As highlighted in our total synthesis of thiomarinol,[4] the residual ethoxy substituent on the product can be extraneous toward several applications, and additional operations are required for its removal. With a view to expand the breadth of this approach, we longed for developing a general method that would circumvent the formation of an acetal and that could be suitable to the preparation of other heterocycles beyond just pyrans. In this regard, our attention was attracted to a report by Masuda and co-workers on the borylation of alkenyl triflate **1**.[5] Instead of the expected alkenylboronate **2**, the authors observed allylic boronate **3** as the major product (eq 2).



Intrigued by this process and encouraged by its potential as a preparative method for heterocyclic allylic boronates, we sought to optimize this formal isomerization toward a catalytic enantioselective formation of allylboronate **3**. This project presented a challenge because the asymmetric isomerization of allylic ethers[6] has been much less successful compared to the analogous isomerization of allylic amines,[7] which is even applied industrially in the ton-scale synthesis of menthol.[8]

A first round of optimization with **1** and pinacolborane (pinBH) was aimed at perfecting the enantioselectivity of allylboronate product **3** while suppressing the formation of alkenylboronate **2**. An initial screen of different chiral ligands and reaction conditions (source of palladium, solvent) revealed that the use of TANIAPHOS[9] (see structure in Figure 1) and $Pd(OAc)_2$ in toluene constituted a good starting point from where to optimize base, temperature, and other parameters. Indeed, as shown in Table 1, we found that the nature of the base has a determining influence on the course and enantioselectivity of this borylation reaction.

Table 1. Optimization of Base and Temperature[a]



entry	base (equiv)	temp (°C)	conversion %[b] 3	conversion %[b] 2	ee of **3** (%)[c]
1	Et_3N (3.0)	80	100	-	56
2	(*i*-Pr)MeN*t*-Bu (3.0)	80	100	-	49
3	DTBMP (3.0)	80	57	28	84
4	*s*-collidine (3.0)	80	35	<5	53
5	proton sponge (1.5)	80	65	35	74
6	$PhNMe_2$ (3.0)	80	84	16	87
7	$PhN(i\text{-}Pr)_2$ (3.0)	80	75	25	78
8	$4\text{-}MeOC_6H_4NMe_2$ (3.0)	80	87	13	79
9	$4\text{-}FC_6H_4NMe_2$ (3.0)	80	-	15	-
10	$PhNMe_2$ (3.0)	25	84	16	86
11	$PhNMe_2$ (0.75)	25	17	62	-
12[d]	$PhNMe_2$ (1.1)	25	86	14	89
13[d,e]	$PhNMe_2$ (1.1)	25	88	12	91
14[d,f]	$PhNMe_2$ (1.1)	25	88	12	92

[a] Reaction conditions: 0.25 mmol of **1** at 0.0625 M. Except in entries 12–14, 1.5 equiv of pinBH were used. See Supporting Information (SI) for detailed procedures. [b] Measured by ^1H NMR (300 MHz in $CDCl_3$) of the crude reaction mixture. The remainder of 100% is unreacted **1**. [c] Measured by chiral HPLC (see SI for details) on the hydrocinnamaldehyde allylboration product **4a** (cf. eq 3a). Absolute configuration assigned by chemical correlation (see SI). [d] 1.1 equiv of pinBH. [e] Solvent is dioxane. [f] Solvent is dioxane, reaction time: 4 h.

While trialkylamine bases effectively suppressed the formation of alkenylboronate **2**, the enantiomeric excess (ee) of desired product **3** was relatively low (entries 1−2). Aromatic amines such as 2-6-di-*tert*-butylmethylpyridine led to a much higher ee, but a substantial proportion of undesired **2** was observed (entry 3). Aniline derivatives were examined next because of their similar basicity to that of pyridines. To our delight, the use of *N*,*N*-dimethylaniline (DMA) led to a clean and reproducible reaction with an optimal enantioselectivity of 87% ee for **3** and only a small proportion of alkenylboronate (**2**) (entry 6). Larger *N*-alkyl substituents led to a lower ee (entry 7) and so did electronic modifications (entries 8−9). With DMA as the optimal base, the effect of its stoichiometry and that of pinBH, as well as the reaction temperature, were examined.[10] The temperature was found to have essentially no effect on the ee of **3** above 25 °C (compare entries 6 and 10). Whereas the use of a single equivalent of base is sufficient, a substoichiometric amount is highly detrimental to the **3**:**2** selectivity (entry 11). The use of a slight excess of pinBH was found

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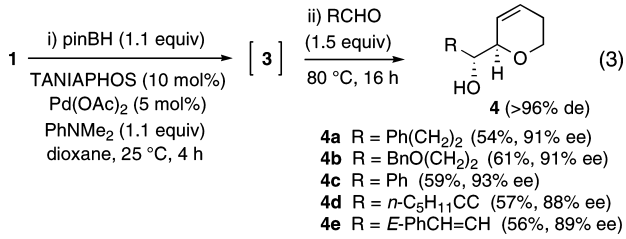
to be suitable, leading to the conditions of entry 12.[11] One last round of fine-tuning[10] examined the influence of solvent, ligand, and reaction time under the provisionally optimal conditions (1.1 equiv of DMA and pinBH, 25 °C, 16 h). Although no diphosphine ligand bettered TANIAPHOS,[10] use of dioxane as solvent led to an improved ee of 91% (entry 13). Furthermore, the reaction is complete within 4 h (entry 14; 92% ee).

Realizing the sensitive nature of allylic boronates, we sought to develop a one-pot borylation/isomerization/allylation protocol that would circumvent the isolation of **3**. This was achieved by simple addition of the aldehyde and increasing the temperature to 80 °C (eq 3). Considering it is a two-stage process, products of representative aldehydes were obtained in acceptable isolated yields and with high stereoselectivity.[12]



(3)

A tentative mechanistic cycle must reconcile the unlikeliness of **2** being an intermediate. The **3**:**2** ratio remains essentially unchanged with temperature and time under the optimal reaction conditions.[10] Moreover, a control using a 50:50 mixture of **1** and **2** as substrates produced **3** and **2** in a 45:55 ratio.[13] Alkenylboronate **2** is the sole product when B_2pin_2 is employed, which suggests the involvement of a Pd hydride species when pinBH is used.[14] Thus, a stereodetermining hydropalladation (**1** to **II** via **I**) may be key to the isomerization to **III** (via β-H elimination) (Figure 1). It would be followed by a stereospecific and regioselective allylic borylation of the reactive intermediate **III** into **3**, via **IV** and **V**. The deuteration pattern of **6** prepared from pinBD and **5** is consistent with this proposed cycle (see box, Figure 1).[10] The role of the base, however, is unclear at this preliminary stage.

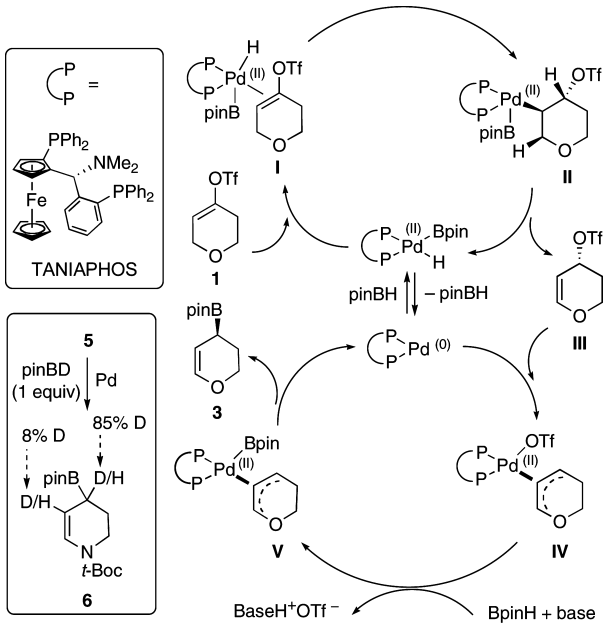
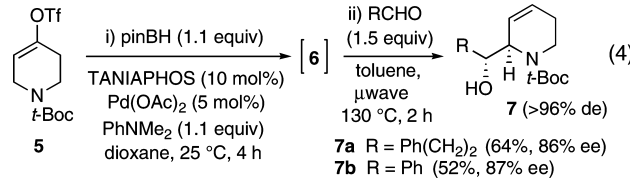


Figure 1. Postulated mechanism for the borylation/isomerization of **1** to give **3**. (Note: the chiral diphosphine ligand was simplified.)

This novel catalytic enantioselective process is proving suitable to prepare other classes of heterocyclic allylic boronates. When subjected to similar conditions, the parent *N*-Boc piperidine **5** provided the allylboration products **7** in good yields with 86% ee (eq 4).[12] Compared to the pyran analogue, the intermediate allylboronate **6** was formed in a lower 4:1 ratio with the corresponding alkenylboronate.[10] Aldehyde allylation with **6** proceeded cleanly under microwave heating. Further optimization could focus on varying the carbamate O-substituent.



(4)

In conclusion, an efficient catalytic enantioselective preparation of heterocyclic allylic boronates was described. The overall borylation constitutes a successful example of formal asymmetric isomerization of allylic ether/amine. Reagents **3** and **6** add to various aldehydes to give useful α-hydroxyalkyl pyrans and piperidines in high stereoselectivity. Applications and extensions of this method are underway.

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Supporting Information Available: Full experimental details, additional tables of optimization studies, chiral HPLC chromatograms, and NMR spectral reproductions for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) See details and additional results in the Supporting Information.
(11) At this stage, one last screen of several Pd sources confirmed that $Pd(OAc)_2$ is the most suitable precatalyst although $Pd(O_2CCF_3)_2$, $Pd(PPh_3)_4$, and $PdCl_2$ were equally efficient.
(12) Unoptimized isolated yields from a reaction scale of 1.0 mmol of **1** or **5**. The ee's of products **4a**, **4c**—**e**, and **7a**—**b** were measured by chiral HPLC.[10] The ee of **4b** was measured by ^{19}F NMR of its Mosher ester.[10] Values for all products are similar within analytical error: it is known that pyranyl allylic boronates similar to **3** (*cf.* eq 1) do not suffer erosion of optical purity in the allylboration process (ref 3b). As in the allylboration of eq 1 (ref 3b), only one diastereomer was identified.
(13) Product **2** was prepared independently according to: Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001–8006.
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