Tandem Oxidations

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Synthesis of 2-Keto-*anti*-1,3-diols by Chemoselective Tandem Oxidation of 2-B(pin)-Substituted Allylic Alcohols**

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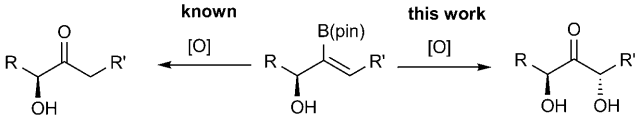
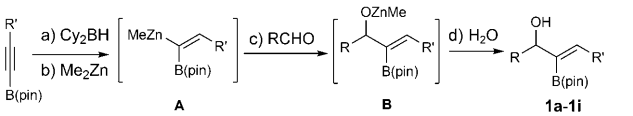
Polyoxygenated hydrocarbons are ubiquitous structural elements in nature.[1–4] An important structural motif within this class is 2-keto-1,3-diols, which are present in numerous natural products and synthetic intermediates.[5–7] Herein we describe a novel stereoselective approach to the synthesis of 2-keto-*anti*-1,3-diols that are difficult or impossible to access using known methods.[5–7] Our approach involves a tandem oxidation of readily accessible 2-B(pin)-substituted allylic alcohols (Scheme 1, right). This tandem oxidation demonstrates that vinyl boronate esters can act as synthons for α-hydroxy ketones, in addition to their well-known role as synthons for ketones (Scheme 1, left).



Scheme 1. Known oxidation of B(pin)-substituted allylic alcohols to 2-hydroxy ketones (left)[8,9] and the diastereoselective oxidation to 2-keto-*anti*-1,3-diols described herein (right).

A crucial step in the development of new synthetic methods is the introduction of reliable and scalable procedures to prepare the substrates. Using our 1-alkenyl-1,1-heterobimetallic reagents, (**A**, Scheme 2) nine new 2-B(pin)-substituted allylic alcohols were prepared on gram-scale in 55–86% yield (Supporting Information, Table S1).[9–13]

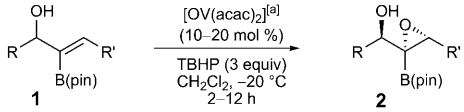
Vinyl boronate esters, including derivatives of those in Scheme 2, readily undergo oxidation at the B–C bond to provide ketones (Scheme 1, left).[8,9,14–18] In the last decade, however, epoxidations of the C=C bond of 4-coordinate vinyl boron derivatives were disclosed[19–21] and, in 2010, Pietruszka and co-workers[22] reported that boronate esters with bulky

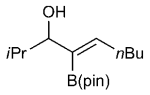
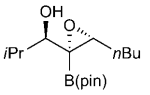
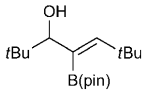
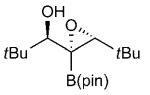
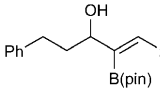
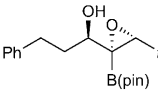
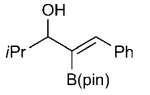
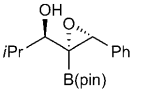
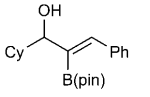
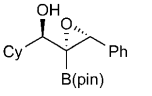
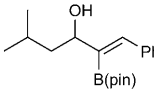
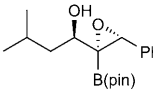
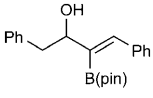
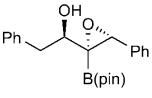


Scheme 2. One-pot synthesis of 2-B(pin)-substituted allylic alcohols through 1-alkenyl-1,1-heterobimetallic intermediates.

enantioenriched auxiliaries could be epoxidized with [OV(acac)$_2$]/TBHP (*tert*-butyl hydroperoxide) (40% yield, 43:57 d.r.) or 200 mol% [Ti(O*i*Pr)$_4$]/DET (diethyl tartrate) (46–65%, >97:3 d.r.).[22]

Table 1: Chemo- and diastereoselective epoxidation of B(pin)-substituted allylic alcohols.



No.	Allylic alcohol		Epoxide		d.r.	Yield [%][b]
1		**1b**		**2b**	>20:1	92[c]
2		**1c**		**2c**	>20:1	83[d] (96[c])
3		**1d**		**2d**	>20:1	85[d,e] (94[c])
4		**1e**		**2e**	>20:1	94[c]
5		**1f**		**2f**	>20:1	96[c]
6		**1g**		**2g**	14:1	85[d]
7		**1h**		**2h**	>20:1	55[d]

[a] 20 mol% V used for entries 2 and 3, rest 10 mol% V. [b] Yields of isolated products. [c] Chromatographic purification was not necessary. [d] Yields after chromatographic purification. [e] Single-crystal structure determination performed.

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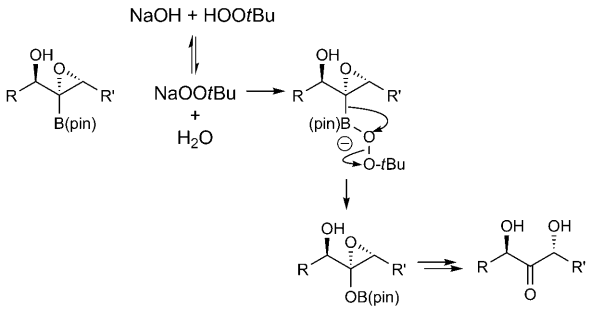
To perform the diastereoselective epoxidation of vinylboronate esters, we initially subjected the allylic zinc alkoxide intermediate (**B**, Scheme 2) to titanium tetraisopropoxide (30 mol%) and TBHP. Under these conditions, the α-hydroxy ketones were isolated (Scheme 1, left) and no B(pin)-substituted epoxides were detected. Two possible explanations for the observed chemoselectivity are: 1) the background reaction of the zinc peroxide with the boron center is too fast or 2) the titanium peroxide is too basic and nucleophilic, resulting in attack on boron rather than epoxidation. To circumvent these issues, we started with the 2-B(pin)-substituted allylic alcohols (**1a**–**1j**) and employed the more electronegative vanadium complex, $[OV(acac)_2]$, to catalyze the directed epoxidation.

Optimization of the $[OV(acac)_2]$-catalyzed epoxidation of 2-B(pin) allylic alcohols was performed and the details are outlined in Table S2. Under the optimized conditions, treatment of the allylic alcohol **1a** with $[OV(acac)_2]$ (10 mol%) and 3 equiv TBHP[23] at −20°C in dichloromethane formed epoxide **2a** as a single diastereomer by ^{1}H NMR spectroscopy. The B(pin)-substituted epoxides decomposed in the presence of trace acid or Lewis acidic silica gel under air. Fortunately, the epoxides formed cleanly and only required filtration through a small pad of silica gel or Celite in most cases (Table 1 and Supporting Information).

The scope of the epoxidation was next determined. When both substituents on the allylic alcohol were aliphatic, the B(pin)-substituted epoxides were isolated in 83–92% yields as single diastereomers (Table 1, entries 1–3). With styryl substrates, epoxides were formed in moderate to excellent yields (55–96%) as single diastereomers (entries 4–7). The yield in entry 7 is lower because chromatographic purification was necessary and resulted in significant product loss due to decomposition. The *anti*-relationship between the hydroxy and epoxide was expected based on minimization of $A^{1,2}$-strain in the directed epoxidation transition states.[24,25] This stereochemistry was confirmed by X-ray structural determination of **2d** (Supporting Information).[26] Although boron-substituted epoxides were generated from metallated epoxides, their reactions with oxidants have not been studied.[27–32]

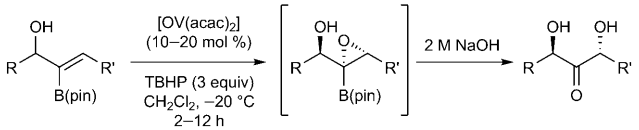
We envisioned that further oxidation of the B(pin) epoxides would provide access to valuable 2-keto-*anti*-1,3-diols.[5–7] Given the sensitive nature of the B(pin)-substituted epoxides in Table 1, a tandem diastereoselective epoxidation/B–C bond oxidation was desired to circumvent their isolation. Thus, after the completion of the epoxidation of B(pin)-substituted allylic alcohols, THF and 2 M NaOH were added to perform the second oxidation (Scheme 3 and Table 2). The mechanism of this oxidation likely proceeds through deprotonation of the TBHP by NaOH, followed by attack of the peroxy species on the unsaturated boron center and migration of the B–C bond. The strained ketal intermediate is expected to undergo hydrolysis to furnish the keto diol.

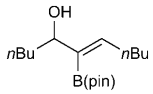
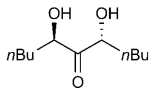
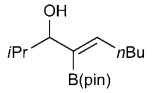
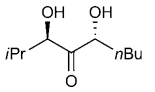
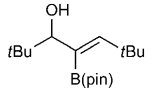
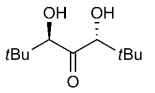
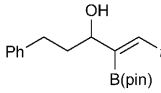
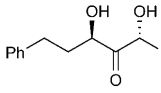
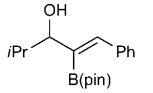
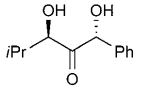
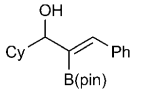
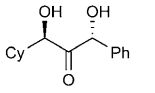
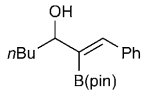
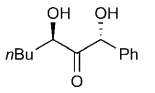
We next examined the scope of the tandem epoxidation/B–C bond oxidation. The tandem oxidation afforded the 2-keto-1,3-diols with good yields and was tolerant of large and small alkyl substituents at the carbinol and on the vinyl group (68–83% yield, Table 2, entries 1–4). Similar yields (60–75%) were obtained with styryl analogues, which resulted in benzylic hydroxy groups (entries 5–7). The second oxidation could also be performed with sodium perborate (entry 3) or hydrogen peroxide (entry 4). Two features of the tandem oxidation reaction in Table 2 should be emphasized; 1) the keto diols were formed as single diastereomers, suggesting that epimerization of the α-carbons did not occur under the basic reaction conditions and 2) that 2-keto-*anti*-1,3-diols containing bulky groups (entries 3 and 4) or aryl substituents (entries 5–7) alpha to the carbonyl would not be accessible



Scheme 3. Proposed mechanism of oxidation of B(pin) epoxides.

Table 2: Tandem vanadium-catalyzed epoxidation/B–C bond oxidation to yield 2-keto-1,3-*anti*-diols.



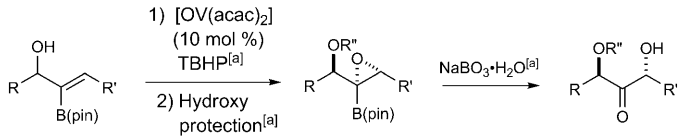
No.	Allylic alcohol		2-Keto-1,3-diol		d.r.	Yield [%][a]
1		**1a**		**3a**	>20:1	68
2		**1b**		**3b**	>20:1	70
3		**1c**		**3c**	>20:1	83[b,c]
4		**1d**		**3d**	>20:1	81[d]
5		**1e**		**3e**	>20:1	60
6		**1f**		**3f**	>20:1	75[b]
7		**1i**		**3i**	>20:1	60

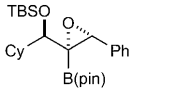
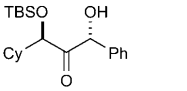
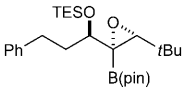
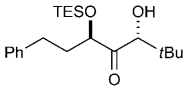
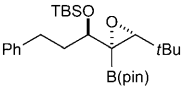
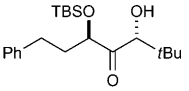
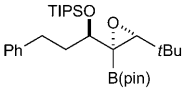
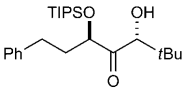
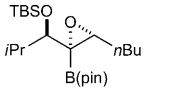
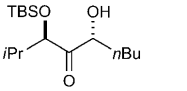
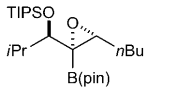
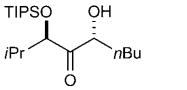
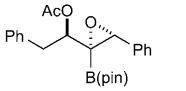
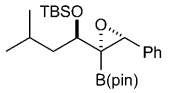
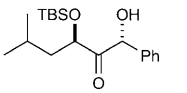
[a] Yields of isolated products. [b] Single-crystal structure obtained. [c] Oxidation with $NaBO_3 \cdot H_2O$, see Supporting Information for details. [d] Oxidation with 30% H_2O_2, see Supporting Information for details.

using the carbonyl α-alkylation chemistry that has been elegantly applied to the synthesis of 2-keto-1,3-diols and natural products.[5,6] Consistent with the mechanism proposed in Scheme 3, the hydroxy groups of **3c** and **3f** (entries 3 and 6) are *anti*, as determined by X-ray crystallography.[26]

Stereoselective elaboration of 2-keto-*anti*-1,3-diol in Table 2 may require chemoselective protection of one of the hydroxy groups, which would represent a significant challenge. To circumvent this issue, we conducted the diastereoselective epoxidation of the B(pin)-substituted allylic alcohols as outlined in Table 1. The resultant epoxy alcohols were then protected in situ with TES, TBS, TIPS and Ac groups (Table 3). With styryl substrates or sterically bulky substrates (R′ = Ph, *t*Bu), the protected epoxides were formed in moderate to good yields (71–84%) as single diastereomers (entries 1–4 and 7). When both substituents on the allylic alcohol are aliphatic, the B(pin)-substituted epoxides were isolated as single diastereomers but in lower yields (41–50%) due to their instability on silica during purification (entries 5 and 6). The acetate-protected B(pin)-epoxide was isolated in 83% yield (entry 7). Careful isolation of B(pin)-epoxide intermediates was followed by oxidation of the B–C bond with sodium perborate leading to formation of the selectively protected 2-keto-*anti*-1,3-diols in 64–83% yield with >20:1 diastereomeric ratio. Of significance, monoprotection of the keto diol **3b** would not favor formation of **8b** or **10b** due to unfavorable sterics. The sequence of epoxidation, protection, and oxidation can also be performed in a tandem fashion as shown in entry 9 (49% yield over three steps).

Table 3: Epoxidation of B(pin)-substituted allylic alcohols followed by protection and oxidation.



No.	Allylic alcohol	Protected epoxide[b]		Yield [%][c,d]	Monoprotected 1,3-ketodiol		Yield [%][c,d]
1	**1f**		**4f**	71		**8f**	70
2	**1d**		**5d**	84		**9d**	81
3	**1d**		**4d**	72		**8d**	77
4	**1d**		**6d**	78		**10d**	81
5	**1b**		**4b**	41[e]		**8b**	64
6	**1b**		**6b**	50[e]		**10b**	83
7	**1h**		**7h**	83		–	–
8	**1g**		**4g**	not isolated		**8g**	49[f]

[a] See Supporting Information for detailed experimental procedures. [b] TBS = *tert*-butyl dimethylsilyl, TES = triethylsilyl, TIPS = triisopropylsilyl, Ac = acetyl. [c] Yields of isolated products. [d] >20:1 d.r. observed in all cases. [e] Epoxides readily decompose on silica during chromatographic purification. [f] Yield for tandem reaction over three steps.

In summary, a variety of 2-B(pin)-substituted allylic alcohols were prepared in one-pot procedures on gram scale. Chemo- and diastereoselective oxidation of 2-(Bpin) allylic alcohols affords *anti*-B(pin)-substituted epoxy alcohols. The epoxidations are catalyzed by [OV(acac)$_2$] and proceed under neutral conditions with excellent diastereoselectivity (>20:1 d.r.) and good to excellent yields (55–96%). The epoxidation can be followed by a base-induced TBHP oxidation of the B–C bond to afford 2-keto-*anti*-1,3-diols with excellent control over the diastereoselectivity. The epoxidation can also be followed by an in situ hydroxy protection and B–C bond oxidation sequence to provide chemoselective monoprotected 2-keto-*anti*-1,3-diols in good yields (64–83% yield, >20:1 d.r.). Previously, vinyl boronate esters were precursors to ketones and 2-B(pin)-substituted allylic alcohols to α-hydroxy ketones.[8,9] Employing the tandem diastereoselective C=C epoxidation/B–C bond oxidation, vinyl boronate esters can now serve as precursors to α-hydroxy ketones and 2-B(pin)-substituted allylic alcohols can be transformed into 2-keto-*anti*-1,3-diols. We anticipate that this method will be useful in the synthesis of polyoxygenated natural products.

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