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Chemo- and diastereoselective tandem dual oxidation of B(pin)-substituted allylic alcohols: synthesis of B(pin)-substituted epoxy alcohols, 2-keto-*anti*-1,3-diols and dihydroxy-tetrahydrofuran-3-ones†

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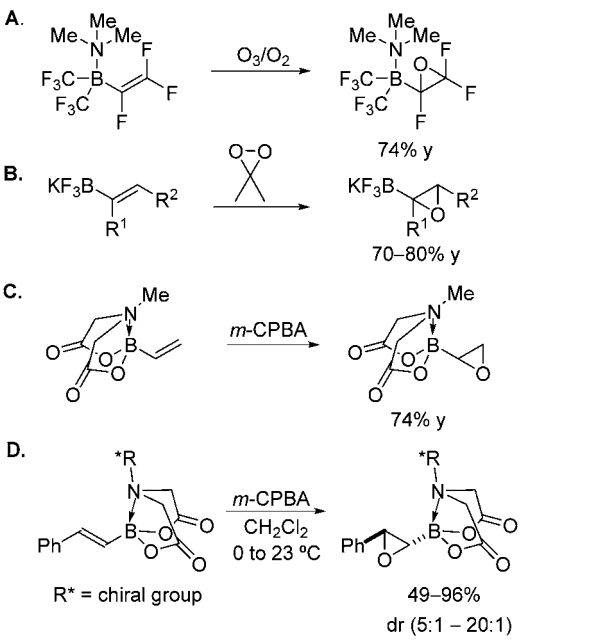
A novel retrosynthetic disconnection for the stereoselective preparation of α,α′-dioxygenated carbonyl compounds is disclosed. Herein we report a method to divert the oxidation of vinyl boronate esters from the B–C bond to the C=C bond, resulting in a new stereoselective class of oxidation products from vinyl boronate esters. Treatment of 2-B(pin)-substituted allylic alcohols with catalytic $OV(acac)_2$ and TBHP resulted in a highly chemo- and diastereoselective directed epoxidation to provide B(pin)-substituted epoxy alcohols (55–96% yield, dr > 20 : 1). In the case of B(pin)-substituted bis-allylic alcohols, highly substituted bis-epoxy alcohols with five contiguous stereocenters were obtained (dr > 20 : 1). Furthermore, the difference in reactivity between allylic alcohols and 2-B(pin)-substituted allylic alcohols towards epoxidation enabled the selective oxidation of the allylic alcohol in the presence of TBHP and $VO(acac)_2$. The reactivity difference between the two allylic alcohols suggests C=CB(pin) to be more electron deficient than C=C(alkyl). The B(pin)-substituted epoxy alcohols are also useful synthetic intermediates. Tandem vanadium catalyzed epoxidation of the 2-B(pin)-substituted allylic and bis-allylic alcohols with excess TBHP generated the intermediate epoxides and bis-epoxides, respectively. Subsequent addition of NaOH resulted in the oxidation of the B–C bond of the B(pin)-substituted epoxides to afford 2-keto-*anti*-1,3-diols (60–83% yield) and epoxide-substituted 2-keto-*anti*-1,3-diols (60–78% yield, dr > 20 : 1). The latter underwent a novel facile acid-mediated cyclization to furnish fully substituted dihydroxy-tetrahydrofuran-3-ones (65–91% yield, dr > 20 : 1). Such compounds are difficult to efficiently access *via* conventional synthetic methods.

1 Introduction

The diverse reactivity of the B–C bond has led to innumerable applications in synthetic organic chemistry.[1–3] One of the most appreciated transformations of the B–C bond is its oxidation to afford alcohols.[4,5] In the case of vinyl boron derivatives, the same oxidation affords ketones. In contrast to these oxidations, there are very few examples demonstrating a reversal of chemoselectivity in the oxidation of vinyl boron species leading to the epoxidation of C=C. One strategy to reverse the oxidation chemoselectivity of vinylboronates is to block oxidation at boron by employing 4-coordinate boron species. Brauer and Pawelke[6] disclosed the epoxidation and oxidative cleavage of $(Me_3N)B(CF_3)_2(CF{=}CF_2)$ with ozone and dioxygen (Scheme 1A).



Scheme 1 Oxidation of four-coordinate alkenyl boron derivatives.

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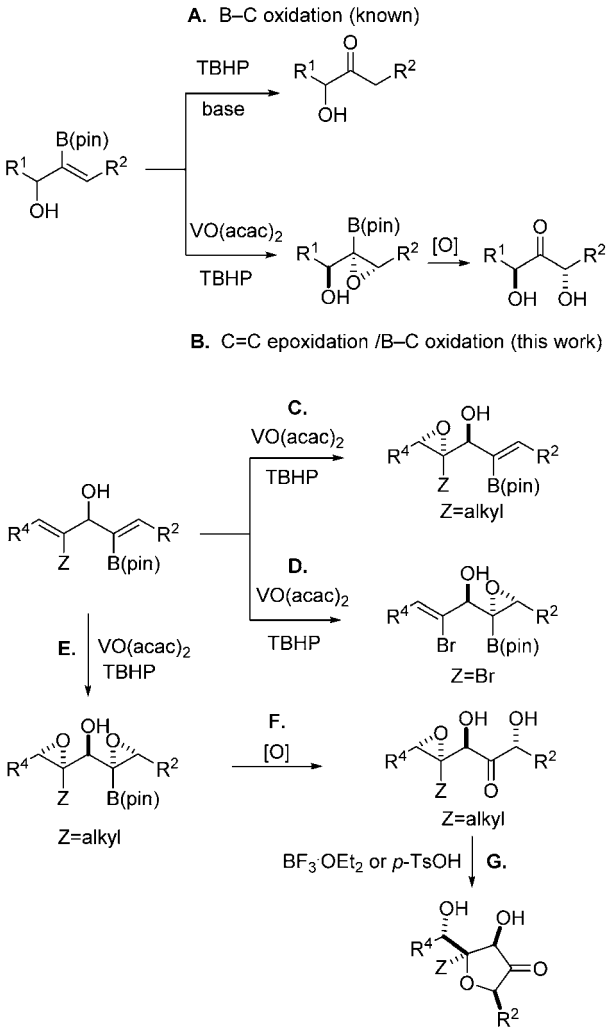
† Electronic supplementary information (ESI) available: Data for new compounds, experimental procedures, copies of ^1H and ^{13}C NMR spectra. CCDC 791005–791007 and 933549. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3sc51616d

In 2003 Molander and Ribagorda[7] demonstrated that vinyl trifluoroborates[3] underwent epoxidation with DMDO to provide epoxytrifluoroborates (Scheme 1B). Uno, Gillis, and Burke[8] showed that vinyl *N*-methyliminodiacetic acid (MIDA) boronates also withstand epoxidation conditions with *m*-CPBA to furnish the terminal epoxide (Scheme 1C). More recently, Burke and Li[9] extended this methodology to the highly diastereoselective epoxidation of internal vinyl boronates bearing an enantioenriched PIDA chiral auxiliary (Scheme 1D).

The results of Pawelke,[6] Molander,[7] Burke,[8,9] and their co-workers raise several interesting questions. These include: (1) is the chemoselective epoxidation of alkenyl boron substrates limited to 4-coordinate boron? and (2) Can the resulting boron-substituted epoxides be useful intermediates in organic synthesis? During our investigation into these questions, Pietruszka and co-workers[10] reported that a 3-coordinate vinyl boronate ester with a bulky chiral auxiliary could be epoxidized (Scheme 2). Poor diastereoselectivity (<2 : 1) and low yields (40–52%) were obtained with achiral epoxidizing agents such as *m*-CPBA and $VO(acac)_2$/TBHP. Use of 2 equiv. $Ti(O\text{-}i\text{-}Pr)_4$, 2.4 equiv. (+)- or (−)-DET, and TBHP resulted in high diastereomeric ratios and moderate yields (46–65%) of the resulting epoxy alcohols.[10]

En route to the current article, we reported the synthesis of 2-B(pin)-substituted allylic alcohols.[11] Under basic conditions, these intermediates underwent chemoselective oxidation of the B–C bond in the presence of TBHP and base (Scheme 3A).[11] Herein, we disclose an approach to reverse the chemoselectivity in the oxidation of vinylboronate esters *via* a highly chemo- and diastereoselective vanadium catalyzed epoxidation of readily available 2-B(pin)-substituted allylic alcohols (Scheme 3B). We probe, for the first time, the relative rates of epoxidation of allylic alcohols *vs.* B(pin)-substituted allylic alcohols using substrates possessing two allylic double bonds (Scheme 3C and D). A sequential diastereoselective epoxidation of the vinylboronate ester followed by B–C bond oxidation to provide 2-keto-*anti*-1,3-diols is introduced (Scheme 3B). When alcohols with both allylic and 2-B(pin)-substituted allylic double bonds were subjected to the tandem oxidation, bis-epoxide intermediates generated *via* pathway E yielded epoxy-substituted 2-keto-*anti*-1,3-diols with high diastereoselectivity (*via* F). Our work here provides novel oxidation chemistry of vinyl boronate esters, which can now be viewed as precursors to both ketones and α-hydroxy ketones.[12,13] Finally, we describe an acid-mediated cyclization of four epoxide-substituted 2-keto-*anti*-1,3-diols (synthesized *via* F, Scheme 3G) to provide fully substituted dihydroxy-tetrahydrofuran-3-ones as single diastereomers. A portion of this work has been previously communicated.[12]

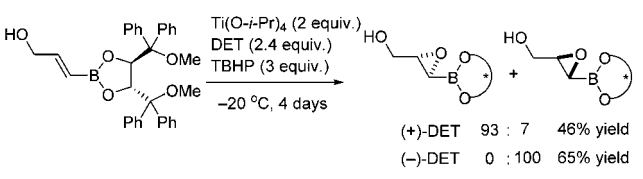


Scheme 3 Known B–C bond oxidation of B(pin)-substituted allylic alcohols (A) and a new class of stereoselective oxidation products *via* chemo- and diastereoselective epoxidation or dual epoxidation/oxidation methodology (B); application of these reactions to unsymmetrical dienols (C–F); an acid-mediated cyclization to dihydroxy-tetrahydrofuran-3-ones (G).

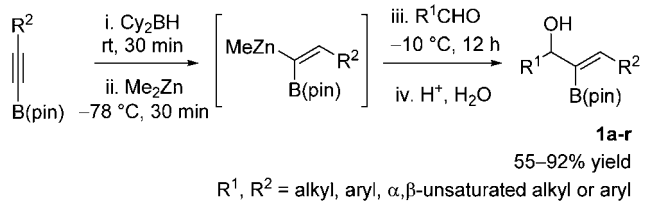
2 Results and discussion

2.1 Synthesis of substrates

We recently reported[11,12,14] a straightforward one-pot synthesis of B(pin)-substituted allylic alcohols *via* functional group tolerant 1-alkenyl-1,1-bimetallic reagents[15] (Scheme 4). Employing air-stable B(pin)-substituted alkynes,[11,14,16,17] hydroboration with



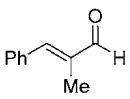
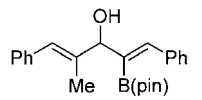
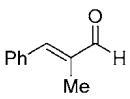
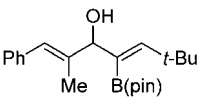
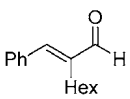
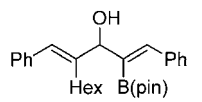
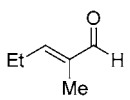
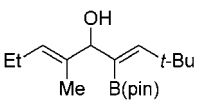
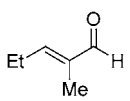
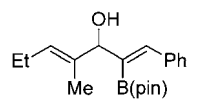
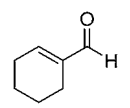
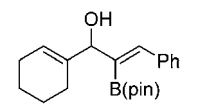
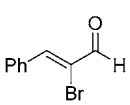
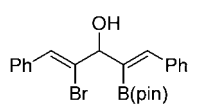
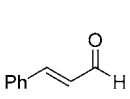
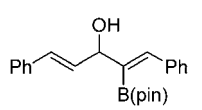
Scheme 2 Pietruszka and co-workers' epoxidation of vinyl boronate esters with stoichiometric Sharpless–Katsuki catalyst.



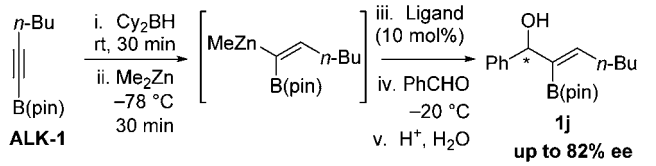
Scheme 4 Generation and trapping of 1-alkenyl-1,1-bimetallic intermediates with aldehydes.

dicyclohexyl borane affords the intermediate 1,1-diboro alkene.[18] The Cy_2B–C bond undergoes transmetallation significantly faster than the (pin)B–C bond,[19,20] because in the latter the p-orbital on boron is partially filled by resonance donation from the adjacent oxygen lone pairs. Thus, transmetallation of the 1,1-diboro alkene with dialkylzinc reagents leads exclusively to the (*E*)-1-alkenyl-1,1-heterobimetallic intermediate, where the Zn–C bond exhibits much greater reactivity than the (pin)B–C bond.[11] Trapping the heterobimetallics with aldehydes and work-up provides the 2-B(pin)-substituted allylic alcohols in 55–92% yield (Scheme 4).[12] The additions in Scheme 4 work well with various aliphatic and aromatic aldehydes as well as with diverse α,β-unsaturated aldehydes. Table 1 contains new bis-allylic alcohol substrates that were prepared for this study. It should be noted that no conjugate addition products were observed. Cinnamaldehyde derivatives typically gave excellent yields (84–92%, entries 1, 2, 7 and 8) whereas aliphatic and cyclic α,β-unsaturated aldehydes gave slightly lower yields (56–71%, entries 4–6). The bis-allylic alcohol substrates in Table 1 were all synthesized on the gram scale.

Table 1 Synthesis of 2-B(pin)-substituted bis-allylic alcohols

Entry	Aldehyde	Allylic alcohol		Yield (%)[ab]
1			**1k**	92
2			**1l**	84
3			**1m**	60
4			**1n**	67
5			**1o**	56
6			**1p**	71
7			**1q**	92
8			**1r**	92

[a] Isolated yields. [b] All substrates synthesized on the gram scale.



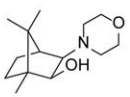
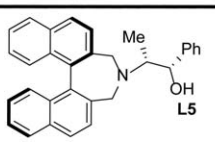
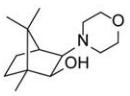
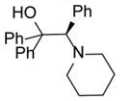
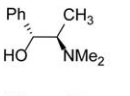
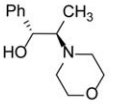
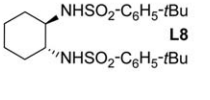
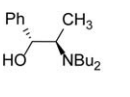
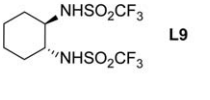
Scheme 5 Asymmetric addition of a 1-alkenyl-1,1-heterobimetallic to benzaldehyde.

2.2 Enantioselective addition of 1-alkenyl-1,1-heterobimetallic reagents to aldehydes

Addition of 1,1-heterobimetallic borozinc intermediates to prochiral aldehydes in the presence of enantioenriched catalysts is expected to lead to optically active 2-B(pin)-substituted allylic alcohols. We have previously demonstrated the utility and versatility of these building blocks in a variety of highly stereoselective transformations.[11,12,14,17,21] Having developed a robust method for alkenyl heterobimetallic additions to aldehydes, we next sought to introduce an asymmetric variant of this reaction, as outlined below (Scheme 5).

β-Amino alcohols form highly enantioselective catalysts in asymmetric additions of organozinc reagents to prochiral aldehydes.[22] One of the premier amino alcohol proligands is Nugent's 2-(*S*)-(−)-3-exo-(morpholino)isoborneol [(−)-MIB] **L1** (Table 2).[23–25] In the presence of catalytic amounts of MIB, organozinc reagents have been employed in the highly enantioselective alkylation,[23,24] vinylation,[26–28] ethoxy vinylation,[29] arylation,[30] and heteroarylation[31] of carbonyl compounds. We,

Table 2 Enantioselective addition of a 1-alkenyl-1,1-heterobimetallic reagent to benzaldehyde

entry	ligand		ee (%)[a]	entry	ligand		ee (%)
1		**L1**	62 (65% y)	6		**L5**	42
2		**L1**	70[b] (70% y)	7		**L6**	82[b] (50% y)
3		**L2**	2	8		**L7**	2[c] (73% y)
4		**L3**	6	9		**L8**	7[c] (73% y)
5		**L4**	49	10		**L9**	12[c]

[a] Addition of aldehyde at −20 °C, using 10 mol% L*. [b] Slow addition of the aldehyde over 30 min at −30 °C. [c] Ligands screened with titanium tetraisopropoxide.

therefore, initiated our search for an enantioselective catalyst for alkenyl borozinc heterobimetallic addition to aldehydes by screening (−)-MIB and several other amino alcohols known to afford high stereoinduction in carbonyl addition reactions.

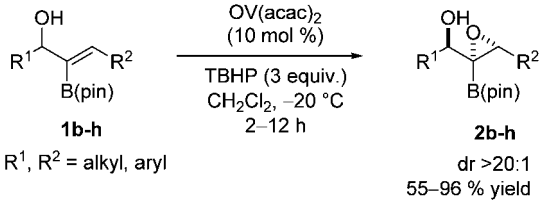
Following hydroboration of the B(pin) alkyne (**ALK-1**) and transmetallation to zinc (Scheme 5), the bimetallic intermediate was added to benzaldehyde in the presence of 10 mol% (−)-MIB at −20 °C. After work-up, the 2-B(pin)-allylic alcohol **1j** was isolated in 65% yield with 62% ee (Table 2, entry 1). Slow addition of the aldehyde over 30 min improved the product ee to 70% (entry 2). The low enantioselectivities in these additions are surprising, because the MIB-based organozinc catalyst generally promotes the vinylation of benzaldehyde derivatives with >90% enantioselectivity. Given that B(pin)-substituted vinyl additions occur readily at −20 °C in the absence of catalyst, and that the enantioselectivity was improved at higher catalyst loading (80–82% ee with >40 mol% MIB), we speculate a fast background reaction was responsible for the poor stereoinduction. Based on this hypothesis, we examined additional catalysts in the addition of heterobimetallic reagents to benzaldehyde.

Ephedrine based amino alcohol ligands have been used in asymmetric vinylations of aldehydes to give allylic alcohols in high enantioselectivity.[20,32] Employing 10 mol% **L2–L4**, however, imparted low enantioselectivities (entries 3–5). Next, we investigated **L5**, a binaphtho-azepine based amino alcohol developed by Chan and co-workers for asymmetric alkynylation of aldehydes.[33] In the presence of 10 mol% **L5**, the product was obtained in 42% ee (entry 6). Ligand **L6** bearing a tertiary alcohol moiety, synthesized by Pericàs[34] and co-workers and known to form a highly enantioselective catalyst, generated the B(pin)-substituted allylic alcohol in 82% ee. Unfortunately the best yield we could obtain at this ee was 50%. We finally investigated a class of bis-sulfonamides, **L7–L9**, which are known to form highly enantioselective catalysts with organozinc reagents in the presence of titanium tetraisopropoxide.[35] In the presence of 10 mol% of bis-sulfonamides **L7–L9**, 1.2 equiv. of $Ti(O\text{-}i\text{-}Pr)_4$ and 1.5 equiv. of Me_2Zn, the resulting bis-sulfonamido-based catalysts failed to provide good enantioselectivities (entries 8–10).

With promising results obtained with (−)-MIB and Pericàs' ligand (entries 1, 2 and 7, Table 2), we attempted to further optimize several reaction parameters such as solvent (toluene, CH_2Cl_2, Et_2O and hexanes) and nature of the alkyl zinc reagents. Despite significant effort, higher enantioselectivities and better yields were not obtained. Based on these results, we chose to proceed with the development of the methods outlined herein with racemic 2-B(pin)-substituted allylic alcohols.

2.3 Chemoselective epoxidation of vinyl boronate esters

With a series of racemic B(pin)-substituted allylic alcohol substrates prepared, we next focused on the chemoselective oxidation of vinyl boronate esters. As mentioned in the Introduction, we had previously shown that treatment of the intermediate allylic zinc alkoxides with TBHP resulted in oxidation of the B–C bond to furnish α-hydroxy ketones.[11] Our hypothesis was that the chemoselectivity of the oxidation could be redirected to favor epoxidation by employing transition metal-based catalysts.



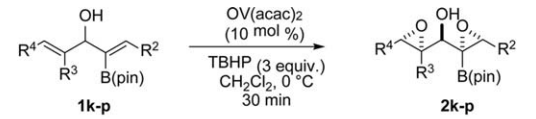
Scheme 6 Chemo- and diastereoselective epoxidation of B(pin)-substituted allylic alcohols.

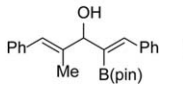
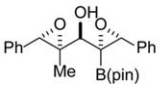
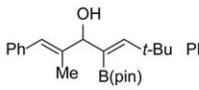
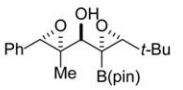
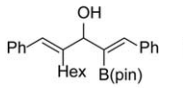
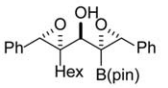
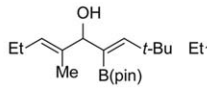
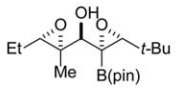
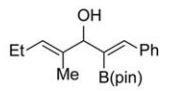
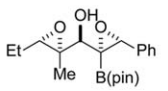
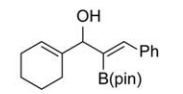
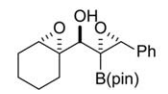
Optimization of the reaction parameters (catalyst, solvent, temperature, stoichiometry, rate of addition, *etc*.) was performed for the $OV(acac)_2$-catalyzed[36] epoxidation of 2-B(pin)-substituted allylic alcohols. The details are summarized in our initial communication.[12] In the presence of 10 mol% of $OV(acac)_2$ and 3 equiv. of TBHP at −20 °C in dichloromethane, the 2-B(pin)-substituted allylic alcohols (**1b–h**) were rapidly converted to 2-B(pin)-substituted epoxy alcohols (**2b–h**) as single diastereomers by ^1H NMR spectroscopy (Scheme 6). Work-up was performed by concentrating the reaction mixture under reduced pressure and rapid purification on silica gel to furnish the B(pin)-substituted epoxy alcohols as single diastereomers, albeit in low yields (typically 30–40%). It was soon realized that these 3-coordinate boron-substituted oxiranes readily decompose in the presence of trace acid or Lewis acidic silica gel under air. Fortunately, the crude products were very clean and required only filtration through a small pad of silica gel or Celite to remove the by-products.

2.3.1 Substrate scope of the epoxidation of B(pin)-substituted allylic alcohols. With the optimized conditions in hand, the scope of the epoxidation of B(pin)-substituted allylic alcohols was examined (Scheme 6). As anticipated from the results above, the B(pin)-substituted epoxides readily decompose even when rapidly chromatographed on silica gel. To maximize the epoxide yields, upon consumption of the B(pin)-substituted allylic alcohols (as judged by TLC), the reaction mixtures were concentrated and the crude products quickly filtered through a pad of silica gel or Celite. This method provided the epoxides in >90% purity (Scheme 6). In several cases the allylic alcohol was converted to the epoxide product without noticeable by-product formation (^1H NMR), facilitating isolation and purification of the B(pin)-substituted epoxides.[12] The *anti*-relationship between the hydroxyl and epoxide is expected due to minimization of $A^{1,2}$-strain in the directed diastereomeric epoxidation transition states.[37,38] The predicted relative stereochemistry was confirmed by single crystal X-ray analysis of **2d** ($R^1 = CH_2CH_2Ph$, $R^2 = t$Bu).

2.3.2 Bis-epoxidation of B(pin)-substituted bis-allylic alcohols. Bis-epoxidation of dienols serves as a route to polyoxygenated compounds. With this in mind, we examined the epoxidation of B(pin)-substituted bis-allylic alcohols using similar conditions as in Scheme 6. The results are depicted in Table 3. Thus, employing 10 mol% $OV(acac)_2$ and 3 equiv. of

Table 3 Chemo- and diastereoselective epoxidation of B(pin)-substituted bis-allylic alcohols



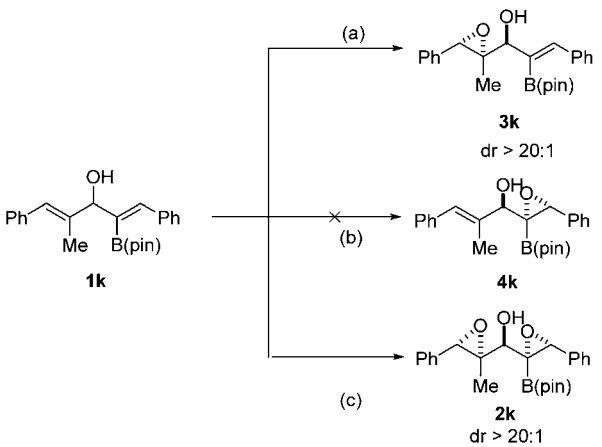
entry	allylic alcohol	product	dr	yield (%)
1.			**2k** >20:1	69[a]
2.			**2l** >20:1	72[a]
3.			**2m** >20:1	86[b,c]
4.			**2n** >20:1	88[c]
5.			**2o** >20:1	90[c]
6.			**2p** >20:1	73[a](82[c])

[a] Yields after chromatographic purification. [b] Reaction took 2 h for completion. [c] Yield determined by ^{1}H NMR analysis of crude mixture with internal standard CH_2Br_2; no chromatographic purification was necessary.

TBHP at 0 °C smoothly epoxidized B(pin)-substituted bis-allylic alcohols to the corresponding B(pin)-substituted bis-epoxy alcohols. It is noteworthy that this bis-epoxidation generates four new stereocenters and furnishes novel bis-epoxides in good yields and excellent diastereoselectivity (dr > 20 : 1).[39] We chose α,β-unsaturated aldehydes with α-substituents that would lead to α-substituted allylic alcohols (Table 3). It is known that epoxidation of allylic alcohols lacking either $A^{1,2}$ or $A^{1,3}$ strain leads to little or no diastereoselectivity.[37,38,40,41] In fact, vanadium-catalyzed epoxidation of bis-allylic alcohol **1r** (Table 1, entry 8) gave a mixture of diastereomers (1.4 : 1) due to lack of either $A^{1,2}$ or $A^{1,3}$ strain in the diastereomeric epoxidation transition states. In contrast, the bis-epoxidations in Table 3 led to single diastereomers in each case (^{1}H NMR). The bis-epoxidation reactions typically required 30 min to reach completion with the exception of **1m**, which required 2 h. The bis-epoxides were obtained in 69–90% yield despite the purification challenges (Table 3).

2.3.3 Chemoselective mono-epoxidation of B(pin)-substituted bis-allylic alcohols. Chemoselectivity is one of the most important challenges in synthetic organic chemistry. The successful epoxidation of both the vinyl groups in B(pin)-substituted bis-allylic alcohols positioned us to probe the chemoselectivity in the vanadium-catalyzed epoxidation of the two vinyl groups in the bis-allylic alcohols **1k–q**. Vinyl epoxy alcohols are versatile synthetic intermediates and have been widely used in the synthesis of natural products, such as *exo*- and *endo*-brevicomin,[42] the anticancer agent EBC-23 found in Australian tropical rainforests,[43] isoaspinonene,[44] and the potent immunosuppressant antibiotic FK506.[45]

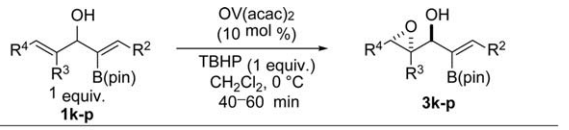
We hypothesized that the electrophilic nature of the oxovanadium(v) peroxide intermediate[46] would enable the catalyst to differentiate between the two vinyl groups based on electronics, favoring epoxidation of the more electron rich vinyl group. Despite the lower electronegativity of boron relative to carbon, the B(pin) group was anticipated to act as a π-acid and remove electron density from the double bond. Furthermore, the large size of B(pin) is anticipated to slow epoxidation proximate to boron. To explore our hypothesis, the relative barriers for epoxidation of model alkenes bearing methyl and boron groups were computed at the B3LYP/6-31G(d)[47] level in the gas phase and at the (M06-2X/6-311G(d,p))[48,49] level in dichloromethane (CPCM; UFF).[50] These preliminary calculations indicate that the epoxidation at the methyl-substituted alkene is more favorable than the epoxidation at the boron-substituted alkene (see ESI† for details). Consistent with the computational study, subjecting the bis-allylic alcohol **1k** to 1.0 equiv. of TBHP in the presence of 10 mol% $OV(acac)_2$ resulted in the chemoselective oxidation of the C=C(alkyl) bond to afford the vinyl-B(pin) substituted epoxy alcohol **3k** with high diastereoselectivity (Scheme 7, path a). No epoxidation of the C=CB(pin) bond was observed. Increasing the amount of TBHP to 1.5 equiv. led to a mixture of mono-epoxide **3k** and bis-epoxide **2k**. As outlined above, further increasing the TBHP to 3.0 equiv. yielded exclusively the bis-epoxide product **2k**. Our optimal conditions entailed slow addition of TBHP over 30 min using a syringe pump to a solution of bis-allylic alcohol **1k** and 10 mol% $OV(acac)_2$ in dichloromethane solvent at 0 °C. The reaction required 40–60 min to reach completion.

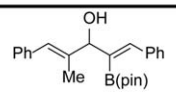
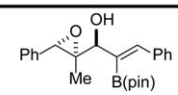
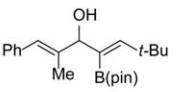
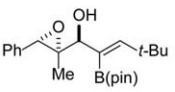
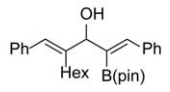
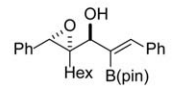
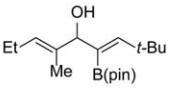
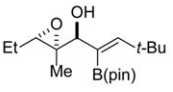
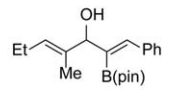
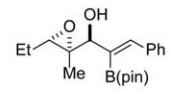
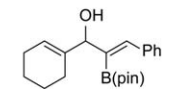
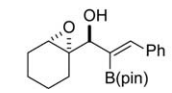


(a) $OV(acac)_2$ (10 mol %), TBHP (1 equiv.), CH_2Cl_2, 0 °C, 60 min
(b) $OV(acac)_2$ (10 mol %), TBHP (1 or 3 equiv.), CH_2Cl_2, 0 °C, 60 min
(c) $OV(acac)_2$ (10 mol %), TBHP (3 equiv.), CH_2Cl_2, 0 °C, 30 min

Scheme 7 Chemo-, diastereo- and regioselective epoxidation of B(pin)-substituted bis-allylic alcohols.

Table 4 Chemo-, diastereo- and regioselective mono-epoxidation of bis-allylic alcohols



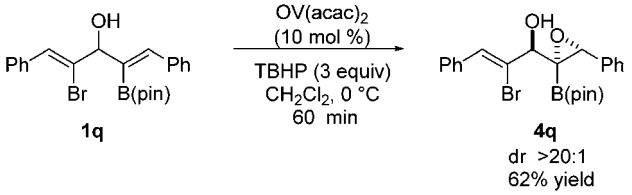
entry	allylic alcohol		product		dr	yield (%)[a]
1.		**1k**		**3k**	>20:1	69[b]
2.		**1l**		**3l**	>20:1	90[b]
3.		**1m**		**3m**	>20:1	70[b](86)[c,e]
4.		**1n**		**3n**	>20:1	63[b](75)[d,e]
5.		**1o**		**3o**	>20:1	54[b,d]
6.		**1p**		**3p**	>20:1	52[b,d]

[a] Isolated yields based on TBHP amount used. [b] Yields after chromatographic purification. [c] 0.8 equiv. of TBHP used. [d] 0.7 equiv. of TBHP used. [e] Yield determined by ^{1}H NMR analysis of crude mixture with internal standard CH_2Br_2; no chromatographic purification was necessary.

Having developed a method for the selective epoxidation of B(pin)-substituted bis-allylic alcohols, we set out to examine the substrate scope of this reaction.

2.3.4 Substrate scope of the mono-epoxidation of B(pin)-substituted bis-allylic alcohols. With the optimized conditions for the mono-epoxidation of 2-B(pin)-substituted bis-allylic alcohols in hand, the scope of the reaction was examined. The epoxidation worked well with methyl and *n*-hexyl substituents at the α-position (entries 1–5, Table 4). For the *n*-hexyl group (entry 3), 0.8 equiv. of TBHP was employed because use of 1 equiv. of TBHP gave mixtures of mono- and bis-epoxy alcohols. Both aromatic and aliphatic B(pin)-substituted bis-allylic alcohols were good substrates. Yields were lower for product **3o** and the cyclohexenyl derivative **3p** due to more challenging purifications *via* silica gel chromatography. Substoichiometric amounts of TBHP (0.7 equiv.) were used in entries 4–6 to avoid formation of bis-epoxides. The *anti*-relationship between the hydroxyl and epoxide is expected due to minimization of $A^{1,2}$-strain in the directed diastereomeric epoxidation transition states.[37–39]

2.3.5 Reversal of chemoselectivity with halide-substituted allylic alcohols. The chemoselective epoxidation of vinyl groups in the presence of vinyl boronate esters led us to ask whether we could manipulate the electronics of the two vinyl groups to redirect the oxidant towards the vinyl boronate ester moiety. We envisioned that an electron deficient vinyl group would steer the reactivity toward the vinyl boronate ester π-system. Preliminary calculations, performed as outlined above, were carried out to predict the relative barriers for epoxidation of model alkenes bearing the boro and bromo groups. The calculations indicated that epoxidation at the boron-substituted alkene is more favorable than epoxidation at the bromo-substituted alkene (see ESI† for details). Therefore, **1q** (Table 1, entry 7) was treated with 3 equiv. of TBHP in the presence of catalytic $OV(acac)_2$. The reaction went to completion with the formation of **4q** in 62% isolated yield as a single diastereomer (Scheme 8).[39]



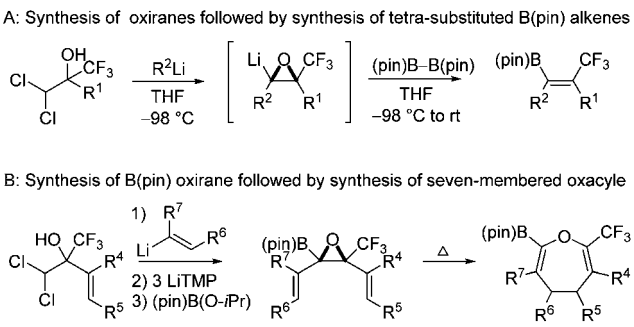
Scheme 8 Chemoselective epoxidation at the vinyl boronate ester moiety of α-bromo-vinyl substituted B(pin) bis-allylic alcohol.

With reliable routes to form the B(pin)-substituted epoxides, we then focused on the development of methods for stereoselective synthesis employing these epoxides as key intermediates.

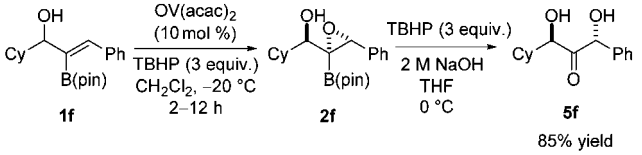
2.4 Oxidation of B(pin)-substituted epoxides

Boron-substituted epoxides are versatile intermediates employed in a variety of novel transformations. They are formed as transient intermediates upon quenching lithiated epoxides with bis(pinacolato)diboron (Scheme 9A).[51–53] The final products of these reactions are olefins,[51,52] diols and triols.[53] Shimizu and Hiyama *et al*. quenched a lithiated epoxide with (pin)B(O-*i*-Pr) and isolated the resulting divinyl B(pin)-substituted epoxide. Upon heating, the epoxide underwent a Cope rearrangement to form a seven membered oxacycle (Scheme 9B).[54] Burke and Li recently employed PIDA-boronate substituted epoxides in the synthesis of small chiral medicinal building-blocks, such as a glucagon receptor antagonist.[9] These reports attest to the diverse reactivity of boron-substituted epoxides.

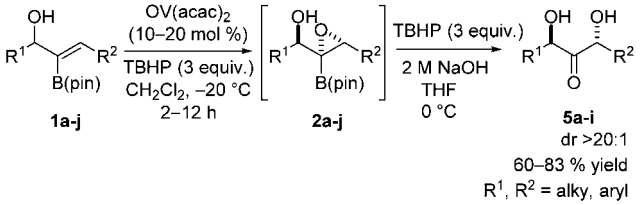
2.4.1 Optimization of the oxidation of B(pin)-substituted epoxy alcohols. With the successful epoxidation of B(pin)-substituted allylic alcohols, we envisioned that further



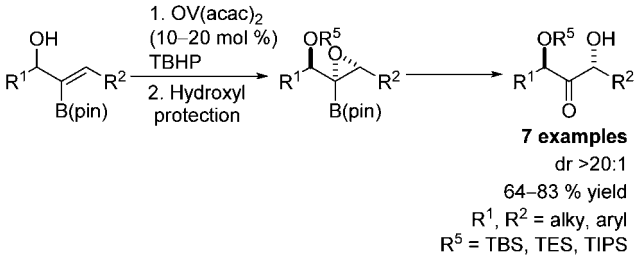
Scheme 9 Stereoselective synthesis of tetrasubstituted alkenyl boronates.



Scheme 10 Oxidation of B(pin)-substituted allylic alcohols to form 2-keto-*anti*-1,3-diols.



Scheme 11 Tandem C=C/B–C oxidation of B(pin)-substituted allylic alcohols to keto diols.



Scheme 12 Epoxidation of B(pin)-substituted allylic alcohols followed by protection and oxidation.

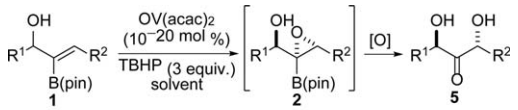
oxidation of the B(pin)-substituted epoxides would provide access to 2-keto-*anti*-1,3-diols. 2-Keto-*anti*-1,3-diols can be precursors for polyoxygenated carbon chains that are common structural motifs in natural products, such as sugars.[55] Given the high sensitivity of the B(pin) epoxides to silica gel, a tandem diastereoselective epoxidation/B–C bond oxidation of 2-B(pin)-substituted allylic alcohols was desired to circumvent the isolation of the epoxide intermediates. Toward development of this tandem reaction, we initially focused on oxidation of the B–C bond in isolated B(pin)-substituted epoxides (Scheme 10). Using 3 equiv. TBHP, the substrate **2f** was treated with 2 M NaOH in THF solvent at 0 °C to cleanly provide the keto diol **5f** in 85% yield. Unfortunately, however, the tandem C=C/B–C oxidation in THF solvent gave multiple products, probably due to complications in the epoxidation step (Table 5, entry 1). Switching to dichloromethane for the $OV(acac)_2$/TBHP epoxidation of **1f** followed by addition of 2 M NaOH to the intermediate epoxide **2f** generated the keto diol **5f**. The oxidation of **2f**, however, was very slow and did not reach completion in 18 h (entry 3). Conducting the epoxidation of **1f** in dichloromethane followed by addition of THF and 2 M NaOH to the intermediate epoxide **2f** resulted in consumption of the epoxide in 8 h and generation of the keto diol **5f** (entry 4). Other oxidants for the B–C oxidation such as aqueous hydrogen peroxide and sodium perborate[5] were evaluated and performed comparably (entry 5–7). With these optimized conditions, we examined the scope of the tandem epoxidation/B–C bond oxidation.

2.4.2 Substrate scope of the tandem epoxidation/B–C bond oxidation. Using the optimized conditions in Table 5 (entries 4, 6 and 7) the tandem reaction afforded keto diols with good yields. Keto diols were tolerant of large and small alkyl and aromatic substituents at the carbinol and in the vinylic positions (60–83% yield, Scheme 11). It is worthy of note that the keto diols were formed as single diastereomers, suggesting that epimerization of the α-carbons did not occur under our basic reaction conditions. The oxidation of the B–C bond most likely proceeds *via* attack of the deprotonated TBHP on the boron and migration of the boron bound carbon to oxygen to form the C–O bond. The strained ketal intermediate then opens with retention of configuration at the newly formed α-carbon. Consistent with this mechanism, single crystal structure determinations of **5c** (R^1, R^2 = *t*Bu) and **5f** (R^1 = Cy, R^2 = Ph) exhibit an *anti*-relationship between the hydroxyl groups.[12] The results indicate that using the same oxidant (TBHP) and directing the initial oxidation to the B–C bond or the C=C bond, either α-hydroxy ketones (Scheme 3A) or 2-keto-*anti*-1,3-diols (Scheme 11) can be prepared with excellent chemoselectivity. The mechanistic difference between the two oxidation reactions allowed us to further couple the chemoselective dual oxidation to a hydroxyl group protection transformation to furnish monoprotected 2-keto-*anti*-1,3-diols (Scheme 12).[12] It would be difficult to obtain the same products *via* chemoselective protection of one of the hydroxyl groups of 2-keto-*anti*-1,3-diol.

2.4.3 Oxidation of B(pin)-substituted bis-epoxides. With a successful tandem epoxidation/B–C bond oxidation, we next turned our attention towards the oxidation of more challenging B(pin)-substituted bis-epoxides **2k–p**, which would provide access to epoxide-substituted 2-keto-*anti*-1,3-diols **5k–p**. Epoxy-keto-1,3-diols are important motifs in biologically active natural products such as Chemomycin A, which possesses antitumor activity against human cancer cells.[56]

For the synthesis of epoxy-keto-*anti*-1,3-diols, B(pin)-substituted bis-epoxy alcohols were generated as shown in Table 3. The crude products were quickly filtered through a pad

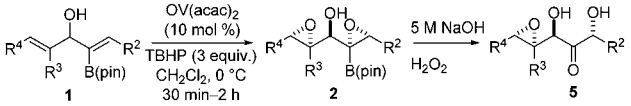
Table 5 Optimization of the tandem epoxidation/B–C bond oxidation

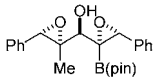
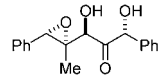
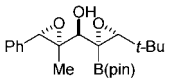
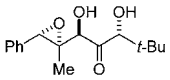
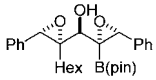
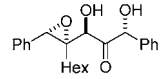
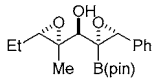
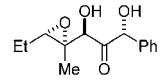
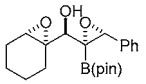
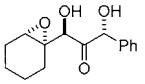


entry	R^1	R^2		solvent	oxidant	yield (%)[a]
1.	Cy	Ph	**1f**	THF	TBHP/NaOH	messy
2.	Cy	Ph	**1f**	Et_2O	TBHP/NaOH	messy
3.	Cy	Ph	**1f**	CH_2Cl_2	TBHP/NaOH	60–70
4.	Cy	Ph	**1f**	CH_2Cl_2/THF	TBHP/NaOH	75
5.	Cy	Ph	**1f**	CH_2Cl_2/THF	H_2O_2/NaOH	60–70
6.	*t*-Bu	*t*-Bu	**1c**	CH_2Cl_2/THF/H_2O	$NaBO_3{\cdot}H_2O$	83
7.	$Ph(CH_2)_2$	*t*-Bu	**1d**	CH_2Cl_2/THF/H_2O	H_2O_2/NaOH	81

[a] Isolated yields.

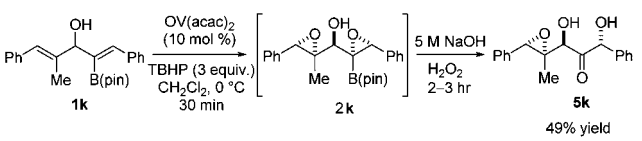
Table 6 Two step oxidation of B(pin)-substituted allylic alcohols to form epoxy-2-keto-*anti*-1,3-diols



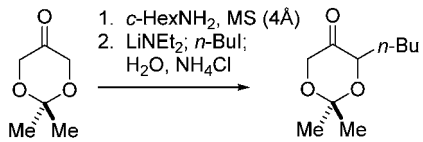
Entry	Bis-epoxide		Epoxide-1, 3-ketodiol		dr	Yield (%)[a]
1		**2k**		**5k**	>20 : 1	78[b]
2		**2l**		**5l**	>20 : 1	78[b]
3		**2m**		**5m**	>20 : 1	64
4		**2o**		**5o**	>20 : 1	60
5		**2p**		**5p**	>20 : 1	61

[a] Isolated yields. [b] Oxidation with $NaBO_3 \cdot H_2O$, see ESI for details.

of silica gel, concentrated and re-dissolved in THF for the subsequent B–C bond oxidation. We evaluated three reagents for the oxidative B–C bond cleavage, namely basic TBHP, sodium perborate and basic hydrogen peroxide. Treatment of substrate **2k** with $NaBO_3 \cdot H_2O$ at rt cleanly provided the epoxy-keto-*anti*-1,3-diol **5k** in 78% yield (entry 1, Table 6). Similar conditions smoothly furnished the bulky *tert*-butyl-substituted epoxy-keto-diol **5l** (entry 2, 78% yield). Using 3.3 equiv. of 30% H_2O_2 and 1.1 equiv. of 5 M NaOH, epoxy-keto-diols **5o** and **5p** were obtained in moderate yields (entries 4 and 5). Comparable results were obtained when treated with basic TBHP (Section 2.4.1); however, the keto diols were obtained in slightly lower yields. Tandem epoxidation/B–C bond oxidation of a B(pin)-substituted bis-allylic alcohol was also examined. Conducting the epoxidation of **1k** in dichloromethane followed by addition of THF, H_2O_2 and 5 M NaOH to the intermediate epoxide **2k** resulted in consumption of the epoxide in 2–3 h and generation of the epoxy-keto-diol **5k** in 49% isolated yield (Scheme 13). The epoxy-keto-diols were again formed as single diastereomers, suggesting that epimerization of the α-carbons did not occur under the basic reaction conditions.[39] Importantly, these epoxy-keto-*anti*-1,3-diols containing bulky *tert*-butyl groups or aryl



Scheme 13 Tandem epoxidation/B–C bond oxidation of a B(pin)-substituted bis-allylic alcohol.



Scheme 14 S_N2-Type α-alkylation of dihydroxyacetone derivatives developed by Enders and co-workers.

substituents (Table 6) cannot be accessed *via* the carbonyl α-alkylation chemistry developed by Enders and co-workers (Scheme 14).[57]

2.5 Diastereoselective synthesis of fully substituted dihydroxy-tetrahydrofuran-3-ones

With reliable routes to synthesize the epoxy-2-keto-*anti*-1,3-diols (Table 6), we then focused on the development of methods for stereoselective synthesis employing these compounds as key intermediates. We envisioned that intramolecular cyclization of our epoxy-keto-diols would furnish fully substituted dihydroxy-tetrahydrofuran-3-ones. Tetrahydrofuran-3-one motifs exist in a variety of natural products, such as scabrolides and pectenotoxins (PTX), which exhibit strong cytotoxic activity against the growth of human cancer cells.[58] Tetrahydrofuran derivatives have also been employed in the synthesis of nucleosides.[59] Tetrahydrofurans and related compounds are typically synthesized by intramolecular cyclization of epoxy alkanols, where the 5-*exo* mode of cyclization is favored due to the low ring strain of the tetrahydrofuranyl alcohol products.[60] Controlling the regio- and diastereoselectivity of the cyclization can be a challenge,

because it is influenced by the nature of the epoxide substrate, reagents and catalysts employed in the reaction.[60] Few other methods for the synthesis of fully substituted tetrahydrofuran-3-ones have been developed. One well-known method of synthesizing tetrahydrofuran-3-ones is the utilization of diazo ketones in the presence of rhodium catalysts. This method frequently gives low yields and mixtures of stereoisomers.[61,62] Substituted tetrahydrofuran-3-ones were also synthesized by singlet-oxygen-mediated reactions using 2-(β-hydroxyalkyl) furans[63] and by radical carbonylation/reductive cyclization using organochalcogen precursors.[62] Both these methods are reported to give inseparable mixtures of diastereomeric furanone products.

We envisioned an acid-mediated cyclization of the epoxy-keto-diols in Table 7 as a route to fully substituted tetrahydrofuran-3-one cores with high dr. Treatment of the epoxy-keto-diol **5k** with $BF_3 \cdot OEt_2$ at rt promoted cyclization to the dihydroxy-tetrahydrofuran-3-one **6k** as a single diastereomer in 90% isolated yield. Compound **6k** is exclusively formed *via* a 5-*exo-tet* cyclization that involves attack of the benzylic alcohol at the congested 3° carbon of the epoxide. Under acid catalysis, it is known that epoxides open *via* attack of nucleophiles at the more substituted carbon atom, and the 5-*exo* mode of cyclization is favored due to the low ring strain of the tetrahydrofuranyl alcohol products. The stereochemistry and regioselectivity of the cyclization were confirmed by X-ray structure determination of **6k** (entry 1, Table 7). The structure exhibits a five-membered tetrahydrofuran-3-one core with inversion at the tertiary carbon center of the epoxide and an *anti*-relationship between the hydroxyl groups (Fig. 1). The acid *p*-TsOH gave similar results (86% yield by ^{1}H NMR), although higher temperature and longer reaction times were required and minor side products were produced. An α-hexyl substrate performed equally well, furnishing the dihydroxy-tetrahydrofuran-3-one **6m** in 91% yield under $BF_3 \cdot OEt_2$ mediated conditions. Both $BF_3 \cdot OEt_2$ and *p*-TsOH conditions were employed in the synthesis of dihydroxy furan-3-ones **6o** and **6p**. In each case, the epoxy keto diols **5o** and **5p** were smoothly transformed into the dihydroxy-tetrahydrofuran-3-ones **6o** and **6p** in 77 and 65% yield, respectively (entries 3 and 4). Product **6p** is interesting in that it contains a spirocyclic ether unit that is found in a number of natural products, including theaspirone isolated from tea,[64] kuroyurinidine from the bulb of *Fritillaria maximowiczii*[65] and numerous others. These oxaspirodecane derivatives exhibit biological activity, as exemplified by muscarinic cholinomimetics.[66] It is reported that syntheses of oxaspirodecane systems suffer from tedious and low-yielding synthetic methods.[66,67] Our approach for the diastereoselective synthesis of dihydroxy-tetrafuran-3-ones thus adds to the synthetic repertoire to access these challenging structural motifs.

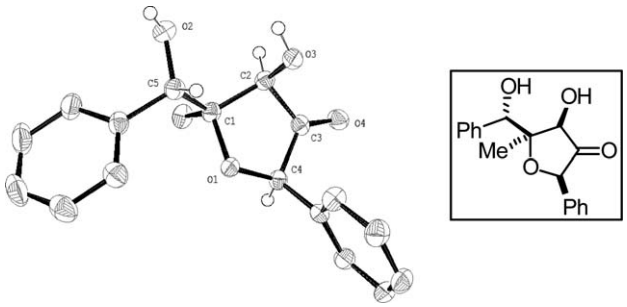
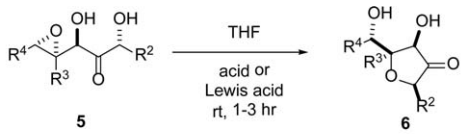
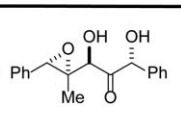
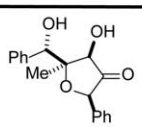
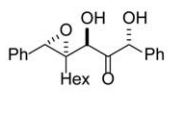
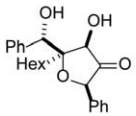
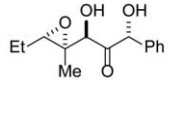
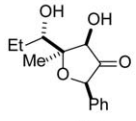
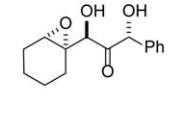
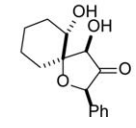


Fig. 1 ORTEP of dihydroxy-hydrofuran-3-one **6k** illustrating the *anti*-relationship of the hydroxyl groups.

Table 7 Synthesis of fully substituted dihydroxy-tetrahydrofuran-3-ones from epoxy-keto-diols



entry	epoxide-1,3-ketodiol	furanone		dr	yield (%)[a]
1.			**6k**	>20:1	90[b]
2.			**6m**	>20:1	91[b]
3.			**6o**	>20:1	77[c]
4.			**6p**	>20:1	65[c]

[a] Isolated yield. [b] $BF_3 \cdot OEt_2$ used. [c] *p*-TsOH in THF/H_2O.

3 Summary and outlook

Chemoselectivity has been called the most challenging problem facing synthetic organic chemists.[68] In the oxidation of vinyl boronate esters with peroxides under basic conditions, it is well known that oxidation occurs preferentially at the B–C bond rather than the C=C bond.[1] We have developed a method to reverse this chemoselectivity. The resulting products are synthetically useful, opening a new manifold of chemistry for vinyl boronate esters.

Outlined herein is the one-pot synthesis of a variety of 2-B(pin)-substituted allylic and bis-allylic alcohols using readily generated 1-alkenyl-1,1-heterobimetallics. Highly chemo- and diastereoselective oxidation of 2-B(pin)-substituted allylic alcohols and bis-allylic alcohols afforded B(pin)-substituted epoxy alcohols and bis-epoxy alcohols respectively, with the latter containing five contiguous stereocenters. The epoxidations were catalyzed by $OV(acac)_2$ and proceeded under neutral conditions with excellent diastereoselectivity (dr > 20 : 1) and good to excellent yields.

We have also investigated the relative rate of epoxidation of the two double bonds in B(pin)-substituted bis-allylic alcohols. By variation of the electronic effect of the two vinyl groups, each can be selectively epoxidized. To the best of our knowledge, this is the first study to probe the relative reactivity of vinyl B(pin) *vs.* alkyl substituted vinyls in epoxidation reactions.

We have also demonstrated that the B(pin)-substituted epoxy alcohols are useful synthetic intermediates. Previously, vinyl boronate esters were precursors to ketones and 2-B(pin)-substituted allylic alcohols to α-hydroxy ketones. Employing the tandem diastereoselective C=C epoxidation/B–C bond oxidation, vinylboronate esters can now serve as precursors to α,α′-dihydroxy ketone motifs. Thus, 2-B(pin)-substituted allylic and bis-allylic alcohols could be transformed into 2-keto-*anti*-1,3-diols and epoxy-2-keto-*anti*-1,3-diols, respectively, after diastereoselective C=C epoxidation/B–C bond oxidations. Given the common place of such polyoxygenated hydrocarbons in natural products, we anticipate that these methods will be useful. Finally, we report a facile acid-mediated ring-opening of epoxide-substituted 2-keto-*anti*-1,3-diols to provide access to fully substituted dihydroxy-tetrahydrofuran-3-ones as single diastereomers. The methods introduced herein provide access to a variety of polyoxygenated compounds that would be difficult to efficiently prepare by other methods.

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