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Borinic Acid Catalyzed, Regioselective Chloroacylations and Chlorosulfonylations of 2,3-Epoxy Alcohols

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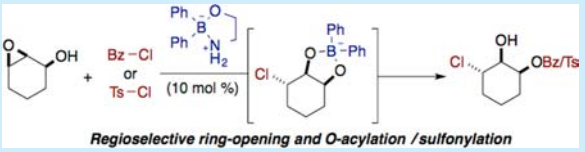
Supporting Information

ABSTRACT: In the presence of a borinic acid derived catalyst, 2,3-epoxy alcohols undergo couplings with acyl and sulfonyl chlorides. This transformation directly generates *O*-acylated or *O*-sulfonylated chlorohydrin diols, with significant levels of regioselectivity for both the ring-opening and *O*-functionalization steps.

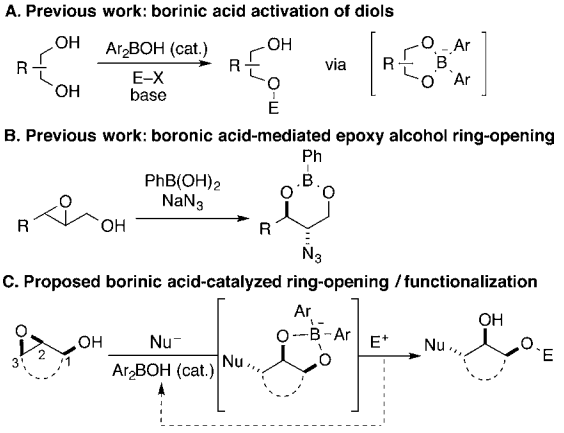


2,3-Epoxy alcohols are versatile building blocks that are readily accessible from allylic alcohols using directed epoxidation methods, including enantioselective variants.[1] While presenting diverse opportunities for synthetic manipulations, the 2,3-epoxy alcohol motif presents challenges in regiocontrol. The problem of regioselective epoxy alcohol ring opening (at C-2 versus C-3) has been studied in depth, and protocols based on the use of Lewis acid promoters and/or electronically biased substrates have been developed.[2] New developments continue to emerge, including the recently reported catalytic methods for ring opening of 2,3-epoxy alcohols.[3] After epoxide opening, a second regioselective transformation is often required to differentiate OH groups in the 1,2- or 1,3-diol product. Chemists have generally tackled these problems in regiocontrol independently, using two-step reaction sequences. Herein, we describe organoboron-catalyzed couplings of acyl or sulfonyl chlorides with 2,3-epoxy alcohols. These transformations directly generate *O*-acylated or *O*-sulfonylated chlorohydrin diols, with significant levels of regioselectivity for both the ring-opening and *O*-functionalization steps.

The present results build on our group's finding that borinic acids (R_2BOH) serve as catalysts for regioselective activation of OH groups in 1,2- and 1,3-diol motifs (Scheme 1A).[4] This mode of catalysis can be used to achieve monoacylations, sulfonylations, alkylations, and glycosylations of di- and triols, including carbohydrate derivatives. Mechanistic studies suggest that the regioselectivity-determining step is the reaction of the electrophile with a tetracoordinate borinic ester generated by reversible covalent binding of a substrate-derived diol group. We speculated that a borinic ester of this type could be generated in an alternative way by borinic acid promoted opening of a 2,3-epoxy alcohol. Precedent for this idea includes the work of Miyashita and co-workers, who employed boronic acids in stoichiometric amounts as promoters of C2-selective ring openings of 2,3-epoxy alcohols (Scheme 1B).[5] If a borinic acid were to accelerate the ring-opening step in a similar way, then the reaction of the resulting borinic ester with an electrophile could close the catalytic cycle, delivering a bis-functionalized product (Scheme 1C).

Preliminary experiments revealed that treatment of *cis*-epoxy alcohol **2a** with benzoyl chloride (BzCl) in the presence of

Scheme 1. Proposed Strategy for Regioselective Ring Opening and Monofunctionalization of 2,3-Epoxy Alcohols



precatalyst **1a** and diisopropylethylamine, conditions that we have employed previously for monoacylations of diols, led to the formation of monobenzoylated chlorohydrin **3a** in 71% yield along with epoxy ester **5a** (Table 1).[3c,6] The *syn* configuration of **3a** was established by X-ray crystallography. In comparison to methods for addition of "silyl–X" reagents across epoxides (e.g., halosilylations,[7] azidosilylations,[8] and cyanosilylations[9]), additions of "acyl–X" are under-developed. The closest precedent for this type of reactivity is the organotin dichloride catalyzed chloroacylation of epoxides reported by Shibata and co-workers.[10]

The effects of varying the conditions for the reaction of **2a** with benzoyl chloride are summarized in Table 1. In addition to epoxy ester **5a**, the C2-chlorinated regioisomer **4a** was observed as a side product under certain conditions. A survey of bases revealed that 1,8-bis(dimethylamino)naphthalene (Proton-sponge) provided superior results to *i*-Pr_2NEt, whereas significantly lower yields of **3a** were obtained using Et_3N, pyridine, and K_2CO_3. In the absence of catalyst, chloroacylation of the epoxy alcohol was

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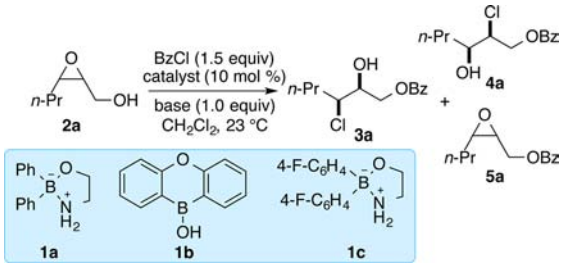
Table 1. Optimization of Conditions for Chloroacylation of Epoxy Alcohol 2a



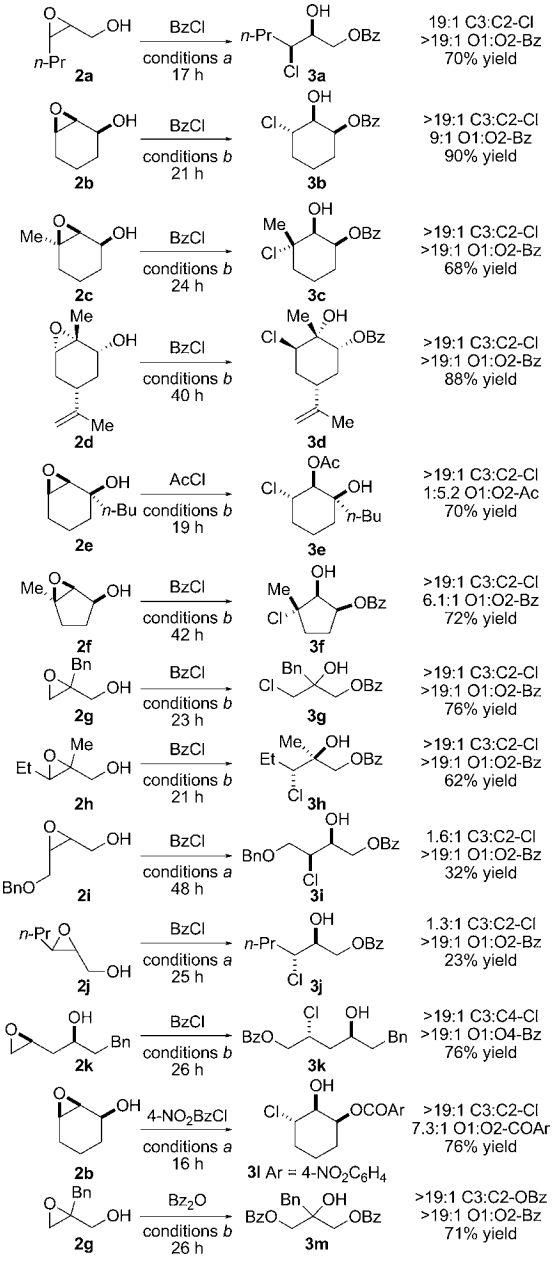
entry	catalyst	base	3a[a]	4a[a]	5a[a]
1	**1a**	*i*-Pr_2NEt	70%	<5%	30%
2	**1a**	Et_3N	35%	<5%	65%
3	**1a**	pyridine	50%	5%	20%
4	**1a**	K_2CO_3	<5%	<5%	15%
5	**1a**	Proton-sponge	80%	5%	10%
6	none	Proton-sponge	<5%	<5%	25%
7	$PhB(OH)_2$	Proton-sponge	<5%	<5%	30%
8	$CeCl_3{\cdot}7H_2O$	Proton-sponge	5%	<5%	40%
9	MgI_2	Proton-sponge	<5%	<5%	25%
10	$Cu(OAc)_2$	Proton-sponge	<5%	<5%	30%
11	Ph_2BOH	Proton-sponge	65%	5%	15%
12	**1b**[b]	Proton-sponge	35%	10%	35%
13	**1c**	Proton-sponge	80%	10%	10%
14	**1a**	Proton-sponge[c]	80%	5%	10%

[a]Yields were determined by ^1H NMR spectroscopy analysis of unpurified reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard. [b]$Bu_4N^+Cl^-$ (1.0 equiv) was added. [c]0.2 equiv of Proton-sponge (1,8-bis(dimethylamino)naphthalene) were used.

not observed, with the product of direct acylation being generated in 24% yield. Other Lewis acid catalysts ($PhB(OH)_2$, $CeCl_3{\cdot}7H_2O$, MgI_2, and $Cu(OAc)_2$) were ineffective in promoting the chloroacylation reaction. The fact that free diphenylborinic acid also catalyzed the formation of **3a** is consistent with the hypothesis that ethanolamine ester **1a** acts a precatalyst. Our previous studies of diol acylation suggest that *N,O*-bis-benzoylation of the ethanolamine ligand triggers entry of **1a** into the catalytic cycle. The amine hydrochloride salt generated upon ligand benzoylation could serve as the initial source of Cl^- for the epoxide ring opening. It may be that the lower yield of **3a** obtained using Ph_2BOH instead of borinic ester **1a** is related to the different Cl^- concentrations generated using these two precatalysts. We have previously reported that heteraborinine-derived borinic acid **1b** displays enhanced activity for certain diol activation reactions, likely due to the high nucleophilicity of its derived borinic esters. This catalyst was inactive under the standard reaction conditions and displayed only modest activity in the presence of $Bu_4N^+Cl^-$. We speculate that the lower Lewis acidity of **1b** relative to Ph_2BOH results in a reduced rate of epoxide ring opening. However, electron-deficient catalyst **1c** did not provide improved results relative to **1a**. The optimized reaction conditions thus involved the use of **1a** as the catalyst and Proton-sponge as the base: we found that the loading of the latter could be reduced from 1.0 to 0.2 equiv without a deleterious effect on the yield.

The chloroacylation protocol was applied to a range of substituted epoxy alcohols (Scheme 2). Depending on the substrate used, either Proton-sponge (0.2 equiv) or *i*-Pr_2NEt (1.5 equiv) as the base provided the best results. The regioselectivity data in Scheme 2 are based on analysis of unpurified reaction

Scheme 2. Chloroacylations of Epoxy Alcohols Catalyzed by 1a[a]



[a]Regioselectivities were determined by ^1H NMR spectral analysis prior to purification. Isolated yields after purification are listed. Conditions *a*: **1a** (10 mol %), RCOCl (1.5 equiv), Proton-sponge (0.2 equiv) CH_2Cl_2, 23 °C. Conditions *b*: **1a** (10 mol %), BzCl (1.5−3.0 equiv), *i*-Pr_2NEt (1.5 equiv), CH_2Cl_2, 23 °C.

mixtures by ^1H NMR spectroscopy. Isolated yields of the major product after purification by silica gel chromatography are listed. *cis*-2,3-Epoxycyclohexanol derivatives **2b−2d** underwent C3-selective epoxide ring opening and benzoylation at O-1. The *trans* relationship between Cl and OH groups was confirmed for product **3c** by X-ray crystallography. Whereas 1-*O*-benzoylation was anticipated on steric grounds for product **3a** (benzoylation of the primary over the secondary OH group being favored), rationalizing the site of acylation in products **3b−3d** is less straightforward. Catalyst **1a** is known to activate the equatorial OH groups of *cis*-1,2-diol motifs in pyranosides.[4] It is unclear

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whether this effect is at play in the synthesis of **3b**–**3d**, or whether the preference for 1-*O*-benzoylation results from deactivation of O-2 by the inductively electron-withdrawing chloro substituent. Tertiary alcohol **2e** was unreactive with BzCl, but the use of a less hindered reagent (acetyl chloride) enabled preparation of the 2-*O*-acylated chlorohydrin **3e**. Steric effects are likely responsible for the anomalous regiochemical outcome of this reaction (acylation at O-2 rather than O-1). A *cis*-2,3-epoxycyclopentanol derivative (**2f**) also underwent efficient chloroacylation in the presence of **1a**.

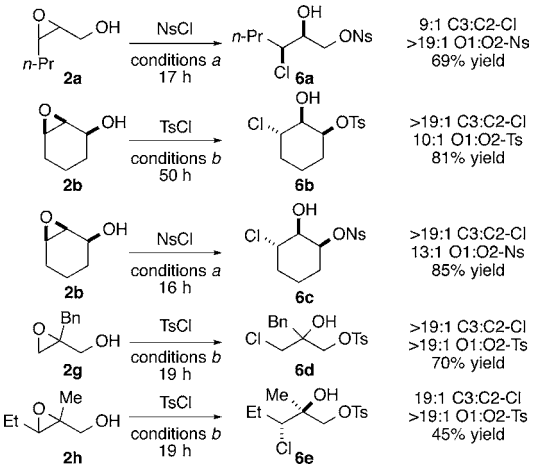
The reactions of substrates **2g**–**2j**, derived from acyclic allylic alcohols, illustrate effects of the identity and position of epoxide substituents on the borinic acid catalyzed chloroacylation reaction. 2-Substituted **2g** and 2,3-disubstituted **2h** were converted to the products of 1,3-chloroacylation with high levels of regiocontrol. However, the ring opening of benzyloxy-substituted *cis*-epoxy alcohol **2i** was less selective than that of unfunctionalized **2a**. Sharpless and co-workers reported that 2,3-epoxy alcohols, ethers, and acetals undergo C3-selective ring openings due to the inductive electron-withdrawing effect of the oxygenated substituents.[2a] In the case of **2i**, the CH_2OH and CH_2OBn substituents exert opposing effects, thus leading to a mixture of C2- and C3-chloro products. It should be noted that the magnitude of the effect observed by Sharpless and co-workers was rather modest, with regioisomer ratios generally not exceeding 4:1. Thus, the borinic acid catalyst acts to enhance the level of selectivity for attack of chloride at C-3. *trans*-Epoxy alcohol **2j** displayed diminished regioselectivity in the ring-opening step relative to its *cis* isomer **2a**. Given that Lewis acid promoted, C3-selective ring openings of *trans*-epoxy alcohols have been reported, a rationale for this difference in selectivities is not apparent. Although the chloroacylation of **2j** was not high-yielding, this transformation demonstrated that the *anti*-diastereomer **3j** was not formed in detectable amounts from the reaction of substrate **2a** (and likewise, that *syn*-configured **3a** was not generated from **2j**). Indeed, diastereomeric side products were not evident in any of the reactions shown in Scheme 2, suggesting an S_N2-type inversion as has been documented for other Lewis acid mediated protocols for preparation of halohydrins from epoxides.

The protocol was applied successfully to 3,4-epoxy alcohol **2k**. The C3-ring-opened product was obtained, as verified by analysis of the chlorine-induced isotope shift in the ^{13}C NMR spectrum.[11] Variation of the acylating agent was also tolerated: coupling with 4-nitrobenzoyl chloride yielded the substituted ester **3l**, and bis-benzoate **3m** was generated using benzoic anhydride in place of BzCl. However, some limitations were encountered in this regard: alkanoyl chlorides and chloroformates (e.g., butyryl chloride, isobutyryl chloride, and benzyl chloroformate) did not give rise to synthetically useful yields of chloroacylation using test substrate **2b**. Attempted fluoroacylation of **2b** using benzoyl fluoride resulted only in the formation of the corresponding epoxy ester.

The use of sulfonyl chlorides under the conditions described above resulted in the formation of monosulfonylated chlorohydrins **6a**–**6e** (Scheme 3). Both *para*-toluenesulfonyl chloride (TsCl) and 4-nitrobenzenesulfonyl chloride (NsCl) were successfully employed in this transformation. The products possess differentiated electrophilic sites in a 1,3-relationship and present opportunities for further selective manipulations.[12]

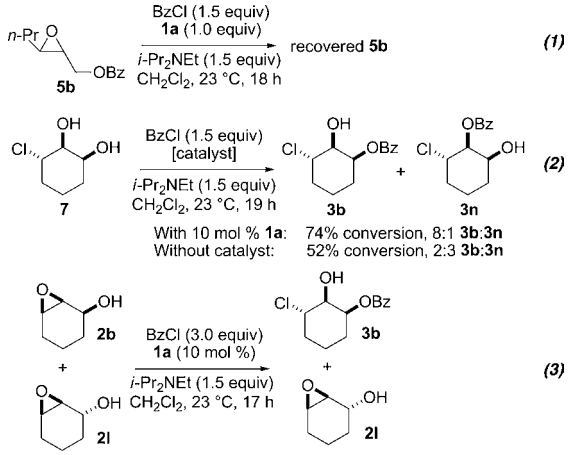
To obtain preliminary information regarding the mechanism of borinic acid catalyzed chloroacylation, the experiments shown in Scheme 4 were conducted. Epoxy ester **5b** was recovered

Scheme 3. Chlorosulfonylations of Epoxy Alcohols Catalyzed by 1a[a]



[a]Regioselectivities were determined by ^1H NMR spectral analysis prior to purification. Isolated yields after purification are listed. Conditions *a*: **1a** (10 mol %), RSO_2Cl (1.5 equiv), Proton-sponge (0.2 equiv) CH_2Cl_2, 23 °C. Conditions *b*: **1a** (10 mol %), RSO_2Cl (1.5–3.0 equiv), *i*-Pr_2NEt (1.5 equiv), CH_2Cl_2, 23 °C.

Scheme 4. Chloracylation of Epoxy Alcohols: Control Experiments



unchanged when subjected to BzCl and *i*-Pr_2NEt, in the presence of either catalytic or stoichiometric quantities of **1a** (eq 1). This result suggests that ring opening precedes alcohol acylation in the catalytic cycle and indicates that the hydroxyl group is necessary for epoxide activation by the borinic acid. Further support for the former point was obtained by subjecting chlorohydrin diol **7** to the reaction conditions, which resulted in the formation of monobenzoate **3b** (eq 2). In the absence of catalyst, the benzoylation of **7** proceeded at a lower rate and with a low level of selectivity for the opposite regioisomer (1.5:1 2-OBz/3-OBz). The borinic acid thus influences the selectivity of the benzoylation step. Finally, *trans*-2,3-epoxycyclohexanol **2l** was inert to the conditions of chloroacylation, presumably due to its inability to interact with the borinic acid through two-point binding (eq 3).

The experiments described above, as well as our mechanistic studies of borinic acid catalyzed reactions of diols, are consistent with the proposed catalytic cycle shown in Scheme 5. Benzoylation of the ethanolamine ligand, which is required for

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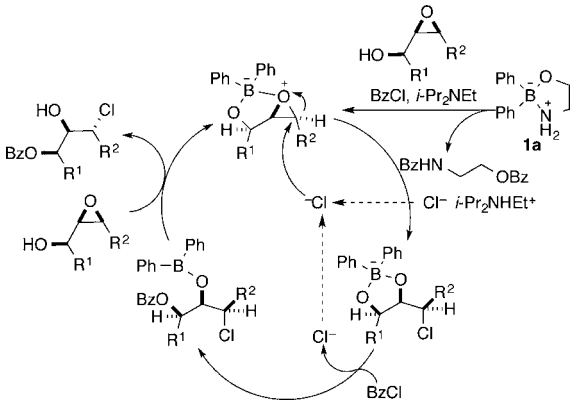
Scheme 5. Proposed Catalytic Cycle



precatalyst activation, serves to generate 2 equiv of i-Pr_2NEt·HCl relative to **1a**. Reversible covalent interaction of the organoboron catalyst with substrate activates the epoxide toward ring opening by the released Cl^-. The observed C3-selectivity is consistent with results obtained for other Lewis acid promoted reactions of epoxy alcohols, including those involving halide nucleophiles.[3c,6] Acylation of the formed borinic ester, and displacement of the product by epoxy alcohol, results in catalyst turnover and regenerates an equivalent of chloride.

In conclusion, an efficient, atom-economical process for regioselective chloroacylation and chlorosulfonylation of 2,3-epoxy alcohols has been developed. In situ acylation or sulfonylation of the chlorohydrin diol not only results in differentiation of the two OH groups but also enables what might otherwise be a challenging catalyst turnover step. The proposed mechanism, involving sequential enhancements of the electro- and nucleophilicity of the bound substrate, highlights the versatile reactivity of borinic acid complexes. Efforts to gain insight into the mechanism of this process, and to extend this mode of catalysis to other sets of reaction partners, are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01541.

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Notes

The authors declare no competing financial interest.

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