

Mild metal-free *syn*-stereoselective ring opening of activated epoxides and aziridines with aryl borates†

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A conceptually new, simple and practical method for the *syn*-nucleophilic displacement of aryl and vinyl epoxides and aryl aziridines with (substituted) phenols, using aryl borates as activating nucleophiles under neutral conditions, is reported.

In general, the reaction of three-membered heterocyclic rings with oxygen nucleophiles is rather difficult, mainly because alcohols, and particularly phenols, behave as poor nucleophilic reagents in substitution processes.¹ Nevertheless, the use of strongly acidic or basic conditions or metal-catalyzed reactions are well-established methods for the corresponding ring-opening reactions, which usually occur in an *anti*-stereoselective way.² In particular, the ring opening of aziridines with poorly nucleophilic *o*-benzenediol (catechol) has not been described, and the use of harsh basic reaction conditions (NaH, EtOH, catechol, reflux) was necessary to obtain the corresponding hydroxy phenols from epoxides.³ Vinyl epoxides are only moderately active alkylating agents under classical displacement conditions, while they are extremely reactive in the presence of some transition metal catalysts.⁴ There are few reports regarding the ring opening of vinyl epoxides by oxygen nucleophiles. Recently, Lautens *et al.* reported a mild rhodium-catalyzed reaction of vinyl epoxides with alcohols, which occurs at room temperature with excellent *anti*-stereo- and 1,2-regioselectivity.⁵ To date, a *syn*-stereoselective ring opening of vinyl epoxides with alcohols has been achieved only by the use of a Pd(0)-catalyst and stannyl alkoxides.⁶ A highly *syn*-stereoselective ring opening of aryl epoxides and aziridines with phenols has not been reported before. Furthermore, it is known that trialkyl borates *do not react* with vinyl epoxides in the absence of a palladium catalyst.⁷

We report here that aryl borates behave as *activating nucleophiles*, and readily react in a *syn*-stereoselective fashion with vinyl and aryl epoxides and with aryl aziridines without the need for a transition metal catalyst. Aryl borates, such as catechol butylborate **1b** and commercially available triphenylborate **1a** are easy to prepare, and have been known for a long time (Fig. 1).⁸

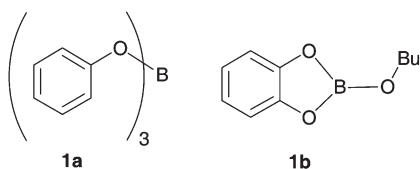


Fig. 1 Aryl borates used as activating-nucleophiles.

In preliminary experiments, we observed that the reaction of catechol borate **1b** with 1,3-cyclohexadiene monoepoxide in a molar solution in THF gave the new *cis*-aryloxy alcohol **2** with complete regioselectivity and a high *syn*-stereoselectivity (*cis:trans* = 94:6, entry 1, Table 1).⁹ A similarly high *syn*-stereoselectivity was obtained with the same substrate, using 1.2 equiv. of triphenylborate **1a** (entry 2), whereas 1,3-cycloheptadiene monoepoxide afforded the corresponding phenoxy alcohol **4** with a lower yield and stereoselectivity (entry 3). The use of (*R*)-styrene oxide afforded aryloxy alcohol **5**, deriving from the regioselective attack of catechol on the benzylic position, with a predominant retention of configuration (entry 4). A completely *syn*-stereoselective ring opening was found in the reaction of *trans*-stilbene oxide with borate **1a** (data not reported in Table 1) and **1b** (entry 5). In the case of liquid borate **1b**, the reaction can be carried out without a solvent.

The rearrangement pathway to ketones was in some cases a consistent side-reaction. With indene oxide, it was possible to completely suppress the undesired formation of 2-indanone by the use of DMF as a solvent for this reaction, giving phenoxy alcohol **7** with a complete *syn*-stereoselectivity and a good yield (entry 6).¹⁰

The introduction of an electron-withdrawing group at the β -carbon is known to retard the isomerization to carbonyl compounds.¹¹ In this respect, *trans* aryl glycidic esters, easily accessible by Darzen reaction, attracted our attention. As shown in entry 7, the ring opening of a glycidic ester with catechol under *neutral* conditions occurred with complete regio- and high *syn*-stereoselectivity, giving the corresponding hydroxy phenol **8** with good yield and without rearrangement side-reactions. It is worth mentioning that the ring opening of glycidic esters with oxygen nucleophiles has not been reported before.

It should be noted that the application of an alternative procedure based on the use of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as the catalyst, successfully described for the addition of alcohols to vinyl epoxides,¹² gave unsatisfactory results when applied by us to aryl and vinyl epoxides in the addition reactions of catechol and phenol.


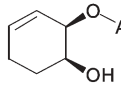
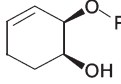
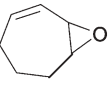
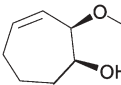

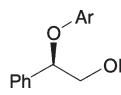
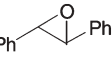
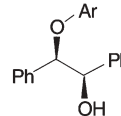
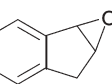
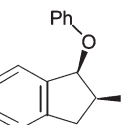
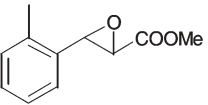
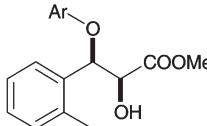
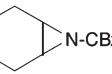
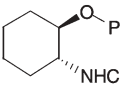
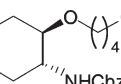
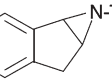
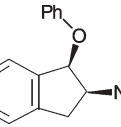
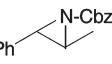
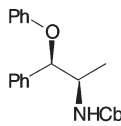
When catechol is used, synthetically useful new hydroxy phenols **2**, **4–6**, **8** can be obtained with fair yields by means of our neutral procedure, without the concomitant formation of the bis-alkylated catechol derivative.³ Hydroxy phenols can be used as precursors of stereodefined 1,4-benzodioxanes,³ a structural feature commonly found in many bioactive molecules.¹³

When simple epoxides, such as cyclohexene and cyclopentene oxides, were allowed to react with borates **1a,b** in THF, a three-component reaction involving the ring opening of THF occurred

† Electronic Supplementary Information (ESI) available: experimental procedures and characterization data for all new compounds. See <http://www.rsc.org/suppdata/cc/b4/b416517a/>

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Table 1 Ring opening of epoxides and aziridines with aryl borates **1a**, **1b**^a

Entry	Borate	Epoxide	Time	Solvent	Product (Ar = <i>o</i> -OH-C ₆ H ₄ -)	<i>syn:anti</i> ^b	Yield ^c	
1	1b		1 h	THF	2		94:6	63
2	1a		1 h	THF	3		92:8	65
3	1b		3 h	THF	4		76:24	38
4	1b		3 h	CH ₂ Cl ₂	5		82:18 ^d	75
5	1b		4 h	neat	6		>95:<5	62
6	1a		1 h	DMF	7		>95:<5	70
7	1b		3 h	THF	8		92:8	82
8	1a ^e		4 h	CH ₂ Cl ₂	9		<5:>95	85
9	1a ^e		3 h	THF	10		<5:>95	42
10	1a ^e		2 h	CH ₂ Cl ₂	11		>95:<5	58
11	1a ^e		2 h	CH ₂ Cl ₂	12		85:15 ^f	40

^a Conditions: see typical procedure. ^b The *syn-anti* stereoselectivity was determined by ¹H NMR and/or HPLC examination of the crude reaction mixtures. For further details, see ESI. ^c Isolated yields of the *syn*-adducts after chromatographic purification (SiO₂). ^d The ratio of retention *vs* inversion of configuration was determined by chiral HPLC. ^e 2.0 equiv. of borate were used. ^f The regioselectivity was 75:25.

(see ESI†). This three-component reaction is reminiscent of the cleavage of cyclic ethers induced by triacetyloxy boranes described by Yamamoto.¹⁴

It is known that phenols can cleave aziridines only under the combined action of a Lewis acid catalyst and microwave irradiation, giving the corresponding phenoxy amines with modest

yields and an *anti*-stereoselectivity.¹⁵ The ring opening of the Cbz-protected aziridine derived from cyclohexene afforded, with borate **1a**, cleanly the corresponding *trans* α -phenoxy *N*-Cbz protected amine **9** when the reaction was performed in CH₂Cl₂ (entry 8). When carried out in THF, a three-component reaction involving the ring opening of THF occurred,¹⁴ giving

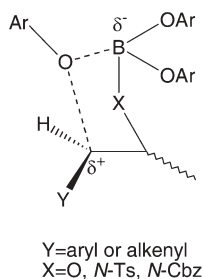


Fig. 2 Plausible mechanism for the observed *syn*-stereoselectivity.

the new *trans* phenoxy(butoxy) *N*-Cbz amine **10** with moderate yields (entry 9). On the other hand, a completely *syn*-stereo- and regioselective ring opening occurred when the *N*-tosyl aziridine derived from indene was allowed to react with borate **1a** (entry 10), and similar results were obtained with borate **1b** (see ESI†). A good *syn*-stereoselectivity was also observed when the Cbz-aziridine of β -methyl styrene was employed, although in this case the regioselectivity in the benzylic position was not complete (entry 11). Unfortunately, all *N*-protected vinyl aziridines examined gave a low yield of mixtures of products.

The fact that an adjacent unsaturation is mandatory to obtain a high level of *syn*-stereoselectivity is a clear indication that the reaction is under electronic control. Probably in the initial step the coordination of the boron to the heteroatom X (X = O, *N*-PG) is followed by a lengthening of the C–X bond, with an advanced formation of a carbocationic species, as depicted in Fig. 2. The internal delivery of the phenoxide anion,¹⁶ initially tethered to the boron atom, occurs preferentially in an entropically favored intramolecular way from the same side of X. Accordingly, whenever the development of a stabilized carbocation is not possible, as for examples with simple aliphatic aziridines and epoxides, a complete *anti*-stereoselective ring-opening reaction is observed.

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- Typical Procedure** as follows: aryl borate **1a** (1.2 mmol) or **1b** (2.0 mmol) was added at rt to a solution of 1.0 mmol of epoxide or aziridine in the appropriate solvent (1.0 mL) (see Table 1) with stirring. The reaction was followed by TLC and was quenched with 5% aqueous HCl (2.0 mL) or 5% aqueous NaOH after the times indicated in Table 1. The solution was diluted with Et₂O or CH₂Cl₂ (30 mL) and washed with brine (3.0 ml) for reactions carried out with borate **1b** and with 5% NaOH for reactions performed with **1a**. Evaporation of the dried organic solution afforded a crude reaction mixture which was subjected to flash chromatography to give the pure compounds **2–12**.
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