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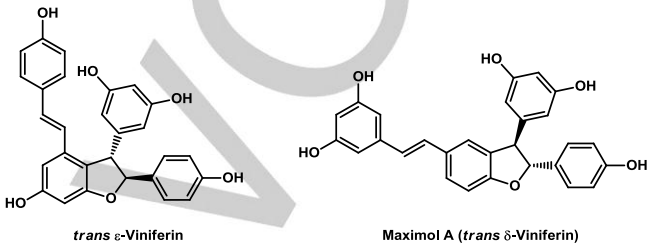
# Regio- and diastereoselective organo-zinc promoted arylation of *trans* 2,3-diaryloxiranes by arylboronic acids: stereoselective access to *trans* 2,3-diphenyl-2,3-dihydrobenzofuran

Teresa Laurita,[a] Lucia Chiummiento,[a] Maria Funicello,[a] Rosarita D'Orsi,[a] Deborah Sallemi,[a] Daniela Tofani[b] and Paolo Lupattelli*[a]

**Abstract:** *Ortho*-oxo substituted *trans* 2,3-diaryloxiranes were regio- and stereoselective arylated by aryl zinc reagents, obtained from the corresponding boronic acids by B-Zn exchange. The reaction was quite general, irrespective to the aryl nucleophile and proceeded *via* a ring opening at the α-carbon with respect to the substituted aryl ring. The stereoselectivity was from high to complete toward the alcohol resulted from retention of configuration at the electrophilic carbon. The method allowed a direct and high yielding access to *trans* 2,3-diphenyl-2,3-dihydrobenzofuran, which is a key structural motif in resveratrol dimers as *viniferins*. The use of enantioenriched starting diaryloxiranes resulted in no loss of stereochemical integrity in the final *trans* 2,3-dihydrobenzofuran, which was characterized for the first time in enantioenriched form.

**Figure 1.** Structures of *trans* ε-Viniferin and Maximol A




*trans* ε-Viniferin  Maximol A (*trans* δ-Viniferin)

## Introduction

The 2,3-dihydrobenzofuran ring-system constitutes the core skeleton of numerous biologically active compounds. Different oligostilbenes having dihydrobenzofuran moieties were isolated from the plant kingdom, in particular from five families, *Vitacee, Leguminose*, *Gnetaceae*, *Dipterocarpaceae* and *Cyperaceae*. They represent resveratrol oligomers[1] and have diverse bioactivities.[2] These so-called "viniferins" have also been found in plants[3] as a result of infection or stress and are supposed to be formed by oxidative dimerization catalyzed by plant peroxidases and/or phenoloxidases. Among the different patterns found for stilbene oligomers, those containing benzofuran[4] or dihydrobenzofuran moiety possess two monomeric units linked by a C-C and a C-O-C linkage.[5] These oligomers demonstrated a significant antioxidant effect and exhibited potent antiplatelet aggregation property. Although the number of individual resveratrol-based natural products is >300, there are many characteristic structural motifs which are conserved among the oligostilbene producing plants. Such metabolites are structurally classified on the base of the regioisomeric mode of their dimerization. One of the main biosynthetic dimerization affords to different 2,3-diaryl-2,3-dihydrobenzofurans, among which *trans* ε-viniferin and maximol A (or *trans* δ-viniferin) are examples (Figure 1).

On a synthetic standpoint the 2,3-dihydrobenzofuran nucleus has recently received significant attention in order to find efficient regio- and steroselective approaches which allow the preparation of good quantities of compounds for broad-spectrum biological and pharmacological analysis.[6] It is worth noting that the hydrogenation of benzofuran derivatives to the corresponding 2,3-dihydrobenzofurans, which might be a reasonably straightforward method to synthesize these compounds, is difficult to achieve with respect to other heteroaromatic nuclei.[7] In fact, the catalytic hydrogenation of benzofuran, under all conditions, is accompanied by partial cleavage of the furan ring. Only recently alternative catalytic hydrogenation and triethylsilane-mediated reduction on a particular 2,3-diaryl-2,3-dihydrobenzofuran were used in the total synthesis of (±) ε-viniferin[8] and its permethylated analogue.[9] Although different synthetic approaches are known for the preparation of the 2,3-dihydrobenzofuran ring-system, few of them are efficient for the synthesis of 2,3-diaryl-2,3-dihydrobenzofurans. Iron-catalyzed oxidative radical cross-coupling/cyclization between phenols and olefins, promoted either by DDQ[10] or di-*tert*-butylperoxide,[11] allowed the preparation some derivatives in moderate to good yield. A biomimetic approach was described by Sako[12] in the diastereoselective synthesis of racemic resveratrol *E*-dehydrodimers by oxidative dimerization, while Che *et al.*[13] reported a ruthenium porphyrin-catalyzed stereoselective intramolecular carbenoid C-H insertion of tosylhydrazones which afforded generally *cis* 2,3-substituted-2,3-dihydrobenzofurans. A programmable, controlled and potentially scalable synthesis of the resveratrol family was described by Snyder, based on the use of a common building block.[14] Even a chemo-enzymatic approach exploiting the laccase-mediated oxidative (homo)coupling of (E)-4-styrylphenols was used for the synthesis of 2,3-dihydrobenzofuran scaffolds.[15] Recently several 2,3-diaryl-2,3-dihydrobenzofurans were prepared utilizing Pd catalyzed one-pot multicomponent reactions and ruthenium-catalyzed intramolecular carbenoid C-H insertions, affording to *cis*/*trans* racemic mixtures, which were resolved by HPLC.[16]

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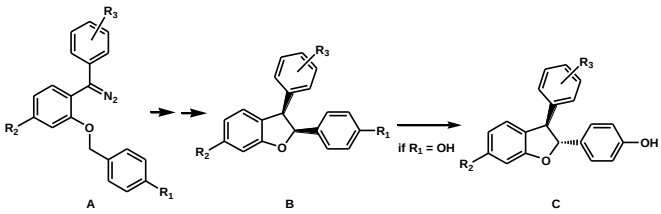
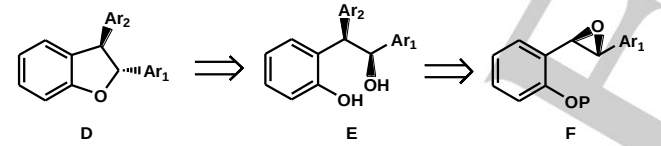
Asymmetric versions of such approaches appeared only recently in the literature. Intramolecular insertion of chiral Rhodium carbenoids from diaryldiazomethanes **A** on benzylic C-H allowed the preparation of different enantioenriched *cis* 2,3-diaryl-2,3-dihydrobenzofurans[17] and the same procedure was used for the first asymmetric synthesis of (*E*)-δ-viniferin. Noteworthy this asymmetric method appears general for the preparation of *cis* derivatives of type **B**, while the isomerization key step to *trans* isomer **C** is driven by the *p*-hydroxyl group on C-2 ring (Scheme 1).

**Scheme 1.** *Trans* 2,3-diaryl-2,3-dihydrobenzofurans from diaryldiazomethanes



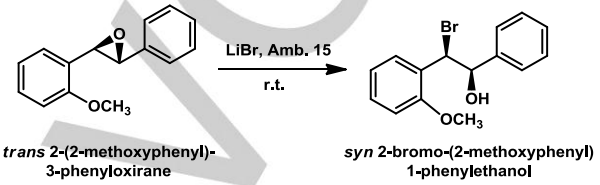

The lack of general stereoselective way to *trans* 2,3-diaryl-2,3-dihydrobenzofurans prompted us to envisage a rapid straightforward route, whose retrosynthetic approach is depicted in scheme 2, starting from *trans* 2,3-diaryloxiranes **F**. The final dihydrobenzofuran **D** could be derived by a Mitsunobu-type cyclodehydration from the suitable hydroxyphenol **E**, which could be formed by a regio- and stereoselective ring-opening reaction of *ortho* substituted diaryloxirane **F** (scheme 2).

**Scheme 2.** Retrosynthetic approach to *trans* 2,3-diaryl-2,3-dihydrobenzofurans




2,3-Diaryloxiranes can be considered non-conventional epoxides in terms of their synthesis and their reactivity. If compared to alkyl ones, they usually show lower reactivity towards nucleophiles and they need some activation by Lewis acids. The particular chemical behaviour of benzyl type carbons in neutral or acidic medium makes them challenging substrates, due to the little differences in reactivity of the two oxiranyl carbons and the possible side reactions such as eliminations or rearrangements.[18] During our studies on nucleophilic ring opening reactions on diaryl epoxides we noted a general stereoretention at the reacting carbon, using different nucleophiles and in the presence of Amberlyst 15 as acidic promoter. Thus both *trans* stilbene oxide[19] and substituted 2,3-diaryloxiranes[20] were stereoselectively converted to the corresponding *syn*-bromohydrins by LiBr/Amb. 15 system. *Trans* 4,5-diaryl-2,2-dimethyl-1,3-dioxolanes were likewise obtained stereospecifically by acetone/Amb. 15 system[21] and this reaction was successfully applied to a calix[4]arene bis-epoxide[22] and to the synthesis of Combretastatine derivatives.[23] Recently the Amb. 15, THF/$H_2O$ system allowed us to prepare chiral *syn*-glycols stereospecifically from the parent *ortho*-substituted *trans* 2,3-diaryloxiranes.[24] The results obtained on substituted diaryloxiranes also showed a dramatic effect of substituent electronic properties on the regioselectivity of the nucleophilic ring opening reaction.[20] In particular, reacting oxiranes with one phenyl ring bearing a strong EWG ($NO_2$, $CF_3$) only one regioisomer was detected, which derived from the opening on the β-carbon with respect to the substituted phenyl ring. On the other hand, in the presence of a strong ERG ($OCH_3$) only the regioisomer derived from an α-opening was observed (Scheme 3).

**Scheme 3.** Regio- and stereoselective ring opening reaction of 2,3-diaryloxiranes with LiBr/Amb. 15.[18]

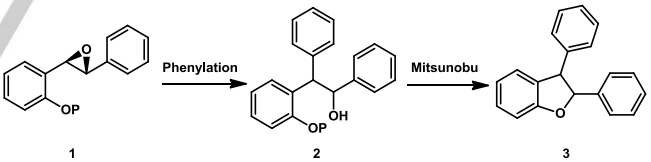



Theoretical calculation confirmed the hypothesis of an acyclic cationic intermediate, suggesting a general chemical behaviour of such substrates, no matter the nucleophile used.

## Results and Discussion

This prompted us to investigate on regio- and stereoselective phenylation of *trans* 2-*ortho*-oxosubstituted phenyl-3-phenyloxiranes **1**, to obtain the corresponding monoprotected hydroxyphenols **2** which, after cleavage of protecting group, could react in the Mitsunobu conditions affording the desired model 2,3-diphenyl-2,3-dihydroxybenzofuran **3** (scheme 4).

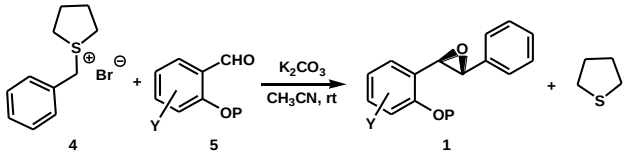
**Scheme 4.** Synthetic route to *trans* 2,3-diphenyl-2,3-dihydrobenzofuran **3**.




Thus, different epoxides **1** were prepared (P = Me, Si(*i*-Pr)$_3$, Bn, EOM) taking advantage of the Corey-Chaykovsky reaction between the suitable *o*-substituted benzaldehyde and a benzylidene sulfur ylide. Such method has proved its efficiency and feasibility in particular toward the synthesis of diaryl epoxides. The direct asymmetric transformation of carbonyl compounds into epoxides using chiral sulfur ylides also offers a complementary and potentially advantageous method over the two-step protocol of Wittig olefination followed by asymmetric epoxidation.[25,26a]

Racemic *trans ortho*-oxosubstituted diaryloxiranes were prepared in good yields and high stereoselectivity from the parent aldehydes **5** using *S*-benzyltetrahydrothiophenium bromide **4** as ylide source and $K_2CO_3$ in acetonitrile, as a modification of Graham procedure[27] (Table 1) (see experimental).

**Table 1. Synthesis of *rac trans ortho*-oxosubstituted 2,3-diaryloxiranes**




4 5 1

| Exp | Ald. | P | Y | Yield (%) | *Trans/Cis* |
|---|---|---|---|---|---|
| 1 | 5a | Me | H | **1a** (80) | 80/20 |
| 2 | 5b | EOM | H | **1b** (90) | 83/17 |
| 3 | 5c | (*i*-Pr)$_3$Si | H | **1c** (75) | *trans* only |
| 4 | 5d | Bn | H | **1d** (78) | *trans* only |
| 5 | 5e | EOM | 5-OMe | **1e** (80) | *trans* only |
| 6 | 5f | EOM | 3-OMe | **1f** (78) | *trans* only |

The reactions were performed using sulfonium/aldehyde 2:1 eq. ratio, at room temperature and 24h as reaction time

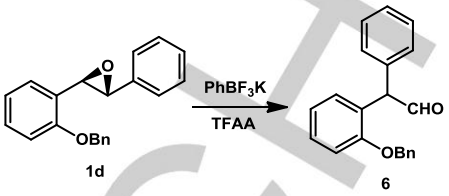
Although the lower electrophilicity of aldehydes **5** the reaction appeared very efficient in terms of chemical yield and stereoselectivity for the preparation of the known epoxides **1a**, **1c**, **1d**[24] (entries 1, 3 and 4) and the new ones **1b** **1e** and **1f** (entries 2, 5 and 6).

Regio-and stereoselective ring-opening reactions performed with carbon nucleophiles have been traditionally limited to the use of stabilized carbanions, strong organometallic reagents and π–rich aromatics.[28] Treatment of terminal epoxides, even enantiomerically pure, with alkyl-, alkenyl-, or aryl-Grignard reagents in the presence of catalytic amounts of a copper salt, or corresponding cuprates, provides a general route to substituted alcohols as building blocks in multistep syntheses.[29] In the case of internal epoxides, with substituents exerting similar steric and electronic effects, the examples are few, showing that this issue represents a great challenge for organic chemists, in particular for substrates which lack an efficient directing group, as 2,3-epoxy alcohols. Moreover, asymmetric catalytic versions of such transformation are difficult because few carbon-centered nucleophiles possess sufficient reactivity to open epoxides without effecting decomposition of the chiral metal catalyst.[30]

The lack of a systematic study on ring-opening reactions of diaryloxiranes with aryl nucleophiles prompted us to test some traditional organometallic systems with the *ortho* benzyloxy substituted epoxide **1d** as model substrate.

Treating **1d** with either PhMgBr or PhLi at room temperature we noted a completely lack of reactivity, at least for the first three hours. The use of CuI/PhMgBr system[31] furnished a complex reaction mixture. On the other hand, by activation of the epoxide with either Amberlyst 15 or $BF_3$,[32] the reaction with PhLi resulted in a mixture of products, whose the main one was diarylacetaldehyde **6**. Again, $PhBF_3K$ in presence of trifluoroacetic anhydride, which was recently successfully used on phenyl glycidates,[33] afforded diarylacetaldehyde **6** as the only reaction product. Such aldehyde represents a typical product of the so-called "Meinwald rearrangement", which is usually promoted by inorganic and organometallic Lewis acids and is often the favoured reaction in the case of diaryloxirane.[34] (scheme 5).

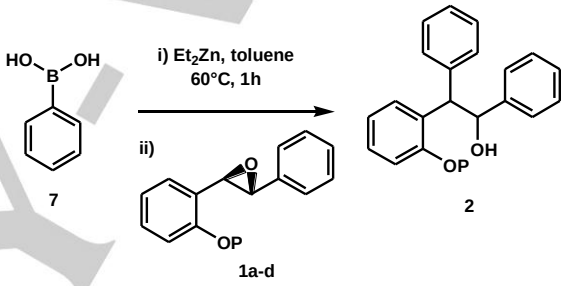
**Scheme 5.** Reactions of **1d** with $PhBF_3K$/TFAA




1d 6

Using the $PhB(OH)_2$/$Et_2Zn$ system, which was recently described in regio- and diastereoselective *C*-arylation of sugar epoxides,[35] good results were obtained with different *o*-oxosubstituted epoxides, as shown in Table 2.

**Table 2. Diethylzinc promoted One-Pot Phenylation of *trans* diaryloxiranes 1 with Phenylboronic acid**




7 1a-d 2

| Exp | P | $PhB(OH)_2$ | $Et_2Zn$ | Yield (%)[a] | syn/anti[b] |
|---|---|---|---|---|---|
| 1 | Me (1a) | 3.0 eq | 10 eq | **2a** (62 | 100/0 |
| 2 | EOM (1b) | 3.0 eq | 10 eq | **2b** (65) | 100/0 |
| 3 | (*i*-Pr)$_3$Si (1c) | 1.5 eq | 4.5 eq | **2c** (65) | 70/30 |
| 4 | Bn (1d) | 1.5 eq | 4.5 eq | **2d** (65) | 100/0 |

[a] 15-20% amount of the corresponding aryl-phenylacetaldehyde was detected. [b] The notation *syn*/*anti* refers to the relative stereochemistry of the incoming phenyl nucleophile and the OH group.

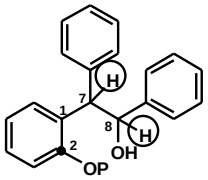
The phenylzinc reagent was generated from phenyl boronic acid and diethylzinc via a facile B-Zn exchange process.[36] The subsequent addition of epoxides **1a-d** resulted in the alcohols **2** in good yield. The reaction was completely regioselective in all cases, being the nucleophilic attack only at the α-carbon with respect to the substituted phenyl ring. These results confirmed our hypothesis of a chemical behaviour of such epoxides, driven by the electronic characteristics of the substituents on the phenyl rings.

Moreover, the stereochemical outcome confirmed the trend for a ring-opening reaction with retention of configuration as favourite pathway. Indeed, the *syn*/*anti* ratio ranged from 7/3, in the case of silyl ether derivative **2c**, to complete stereoselectivity toward *syn* compound, in all other cases**.**

***Characterization of compounds* 2**.

Since 2-aryl-1,2-diphenylethanols **2** are not described in literature, an unambiguous characterization had to be given.
The structure **2**, as single regioisomer, was confirmed for all the products obtained, by careful $^{1}H/^{13}C$ NMR analysis: once carbons and hydrogens at the side chain have been assigned by direct $^{1}H/^{13}C$ correlation experiments, a long-range $^{1}H/^{13}C$ correlation between the C2 carbon and the proton at C7 was observed for all the products obtained. No correlation was observed between C2 and the proton at C8, which had been assigned to C*H*(OH)[37] (Figure 2).

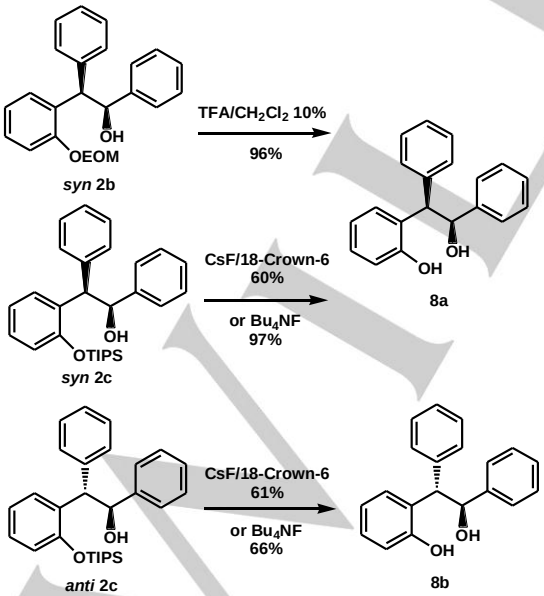
**Figure 2**. Diagnostic correlations between $^{1}H$ and $^{13}C$ NMR signals of structures **2**: C7-*H* and *C2* were correlated while C8-*H* and *C2* were not.




**2**

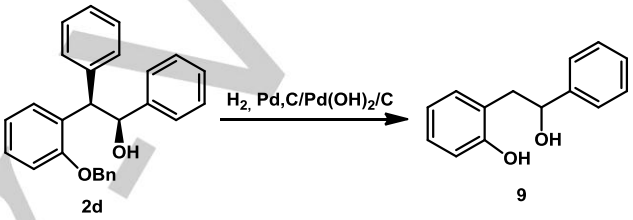
With the desired regioisomers in hand different deprotection reactions were investigated, to afford the suitable hydroxyphenols for the last Mitsunobu type cyclodehydration reaction. The reactions were run with all the products obtained, since they were also useful for the identification of the relative stereochemistry of compounds **2**. Attempts to perform demethylation reaction on **2a** with $BCl_3$ or $BF_3{\cdot}Et_2O$ resulted in a complex reaction mixture. On the other hand **2b** was treated with 10% TFA/THF mixture at 0°C and the corresponding hydroxyphenol **8a** was obtained in good yield (scheme 6).

**Scheme 6.** Deprotection reactions on **2b** and **2c**.



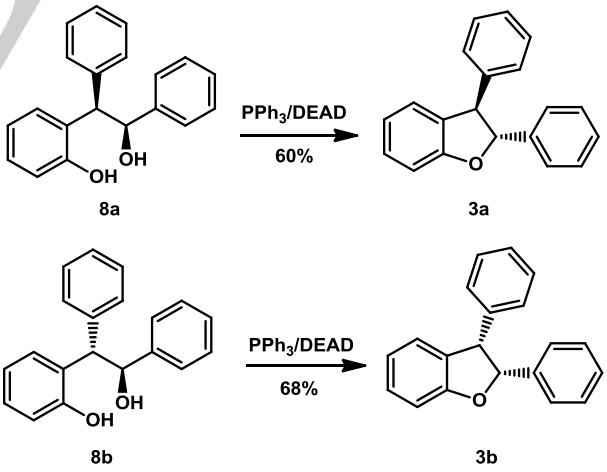

Tri-isopropylsilyl ethers are usually much more sterically demanding and stable than simple silylethers. They are inert toward many oxidants, reductive agents and Lewis acids, while fluoride sources are often the reagents of choice for their cleavage.[38] Using either *n*-$Bu_4F$ in THF[39] or the CsF/18-Crown-6 system[40] both ***syn*-2c** and ***anti*-2c** were transformed into the corresponding *syn* and *anti* hydroxyphenols **8a** and **8b**, respectively, in good yield, with *n*-$Bu_4F$ being the most efficient reagent in both cases. The benzyloxy derivative **2d** appeared unexpectedly inert toward the most common deprotection procedures. After numerous unsuccessful attempts using $H_2$/Pd,C (10%) in different reaction mediums, Pd,C (10%)/$HCOONH_4$[41] or $NiCl_4/NaBH_4$[42] systems, the substrate was successfully reacted with $H_2$, Pd/C (10%), $Pd(OH)_2$/C (50%) system in THF/*i*PrOH (3:1).[43] Unfortunately hydroxyphenol **9**, derived by a cleavage of both benzyl and phenyl groups on C2 at the side chain, was the only product observed (scheme 7).

**Scheme 7**. Attempt of deprotection of **2d**.




The hydroxyphenols **8a** and **8b** were finally submitted to $Ph_3P$/DEAD in THF[44] affording the corrsponding *trans* and *cis* 2,3-diphenyl-2,3-dihydrobenzofurans **3a** and **3b**, respectively, in high yield (scheme 8).

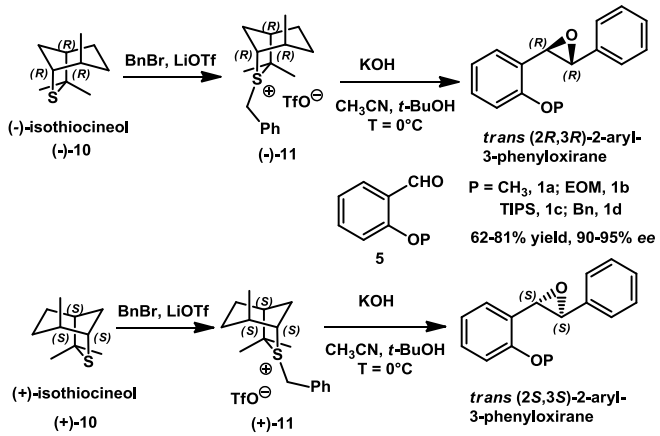
**Scheme 8.** Access to *trans* and *cis* 2,3-diphenyl-2,3-dihydrobenzofuran **3a** and **3b.**




The NMR spectra of the products were compared with those described in literature[16] and confirmed the stereochemistry of both. Thus, the relative stereochemistry of all the intermediates **2b**, **2c**, **8a** and **8b** was indirectly confirmed as well.[45]
The availability of isothiocineol **10**[26] in both enantiomeric forms, either commercial or easily prepared, allowed us to prepare also *ortho*-substituted diaryloxiranes in high yield and excellent *ee* by first *in situ* deprotonation of benzylsulfonium salt **11** of

isothiocineol with KOH and subsequent reaction of the ylide with the suitable *ortho* substituted benzaldehyde (scheme 9).

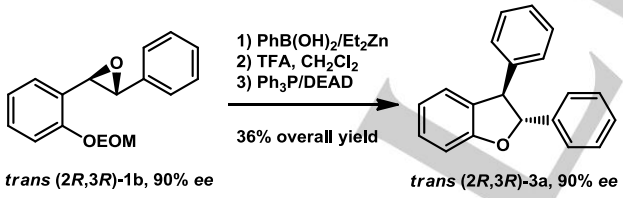
**Scheme 9.** Preparation of enantiopure diaryloxiranes




The yield was from discrete to excellent and the *ee* was high in all cases.

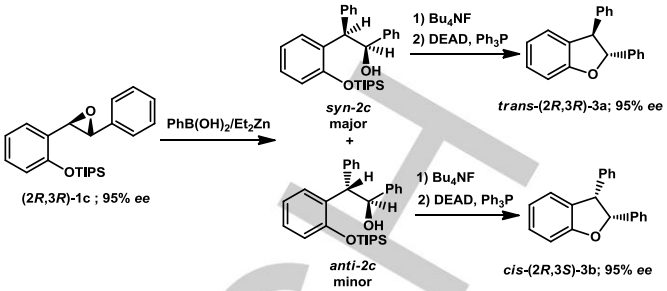
Thus, the synthetic pathway was successfully repeated for homochiral epoxides **(2*R*,3*R*)-1b** and **(2*R*,3*R*)-1c** affording the corresponding homochiral *trans* and *cis* 2,3-diphenyl-2,3-dihydrobenzofurans. The initial *ee* of the starting epoxides was maintained in the final products and in the intermediates throughout the synthesis. It is worth noting that homochiral *trans* (2*R*,3*R*)-2,3-diphenyl-2,3-dihydrobenzofuran (***trans* (2*R*,3*R*)-3a**) was prepared for the first time in high *ee* and good overall yield from the suitable epoxide **(2*R*,3*R*)-1b**, easily obtained from protected salicylaldheyde, benzyl bromide and isothiocineol as chiral source (scheme 10).

**Scheme 10.** Access to *trans* (2*R*,3*R*)-2,3-diphenyl-2,3-dihydrobenzofuran (***trans* (2*R*,3*R*)-3a)**.




The same route was successfully applied to **(2*R*,3*R*)-1c** giving rise to homochiral *trans* and *cis* dihydrobenzofurans **3a** and **3b** (scheme 11).

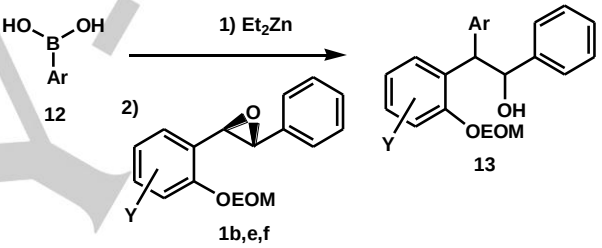
**Scheme 11.** Synthesis of homochiral *trans* and *cis* **3a** and **3b** from **(2*R*,3*R*)-1c**




In particular, comparison of HPLC analysis with chiral phase and optical activity of **3b** with those described in literature[17b] confirmed its absolute configuration as well as those of the other intermediates and final products **2b**, **2c**, **8a**, **8b** and **3a**.

As natural development of the investigation the substrate scope of the opening reaction was tested using various aryl boronic acids as nucleophilic source and epoxide **1b** as electrophilic acceptor. The results are given in Table 3.

**Table 3**. Substrate scope of Arylboronic Acids for ring-opening reaction of *trans* 2-(2-ethoxymethoxyphenyl)-3-phenyloxirane **1b.**




| Exp | Ar | Y | Prod | Yield (%) | *syn*/*anti*[a] |
|---|---|---|---|---|---|
| 1 | 4-BrPh (12a) | H (1b) | 13a | 65[b] | 100/0 |
| 2 | 3-$CF_3$Ph (12b) | H (1b) | 13b | 55[b] | 100/0 |
| 3 | 4-OMePh (12c) | H (1b) | 13c[c] | 60 | mixture[c] |
| 4 | 3-FPh (12d) | H (1b) | 13d | 50[b] | 80/20[d] |
| 5 | 3-OMePh (12e) | H (1b) | 13e[e] | 62 | 35/31 (34)[d,e] |
| 6 | 2-Benzothienyl (12f) | H (1b) | 13f | 60 | 100/0 |
| 7[e] | 4-BrPh (12a) | 5-OMe (1e) | 13g | 65 | 84/16 |
| 8[e] | 4-BrPh (12a) | 3-OMe (1f) | 13h | 66 | 100/0 |

[a] The notation *syn*/*anti* refers to the relative stereochemistry of the incoming aryl nucleophile and the OH group. [b] 15-20% amount of the corresponding aryl-phenylacetaldehyde was detected. [c] Equimolar mixture of the four possible products was obtained. [d] Diasteroisomeric ratio determined from $^1$H NMR of the purified mixture. [e] Equimolar quantity of the other regioisomer (probably *syn*) was detected in the NMR spectra of the mixture.

As it can be seen, the reaction appeared almost general affording the corresponding *syn* arylalcohols **13** exclusively, in acceptable yield in the case of bromophenyl-, trifluoromethylphenyl-, and benzothienylboronic acids (**12a**, **12b**

and **12e**, entries 1,2 and 5). In the case of 3-fluoro derivative **12d** the corresponding product **13d** was obtained as promising 80/20 *syn*/*anti* mixture (entry 4). Only in the case of 4-methoxyphenylboronic acid **12c** the regio- and stereoselectivity of the reaction dropped dramatically, affording an equimolar mixture of the four possible ring opening products. Better results were achieved using 3-methoxyphenylboronic acid **12e** and almost equimolar mixture of *syn*/*anti* **13e** and the other regioisomer (probably *syn*) was obtained. This last result appeared quite unexpected suggesting for the first time an effect of the nucleophilic character of the incoming reagent on the selectivity of the reaction. Dioxofunctionalized epoxides **1e** and **1f** were also tested with 4-bromophenylboronic acid **12a** affording the corresponding *syn* arylalcohols **13g** and **13h** with good yield and high selectivity. Thus the method appears of wide scope in the preparation of polyfunctionalised *trans* 3-aryl-2-phenyl-2,3-dihydrobenzofurans.

**Conclusion**

A series of *ortho* oxo substituted *trans* diaryloxiranes was regio- and stereoselectively opened by $PhB(OH)_2/Et_2Zn$ system, allowing stereoselective access to *trans* 2,3-diphenyl-2,3-dihydrobenzofuran with no loss of optical purity of the starting epoxide. The method appeared quite general with different aryl nucleophiles, thus representing a powerful tool for the preparation of new substituted *trans* 3-aryl-2-phenyl-2,3-dihydrobenzofurans.

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**Keywords:** diaryloxiranes, aryl zinc reagents, ring opening reaction, 2,3-dihydrobenzofurans

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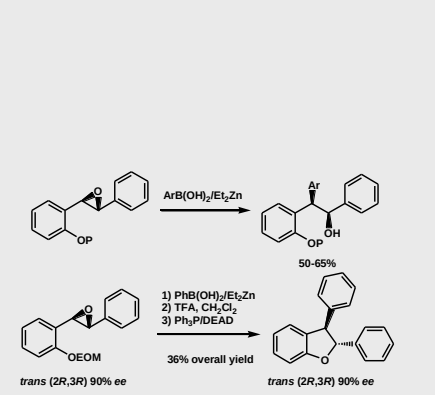
[45] Comparison of $^1H$ NMR spectra of compounds **2** suggested the *syn*-**2d** as major product and *anti*-**2d** as minor one, as written in Table 2

## Entry for the Table of Contents

Key Topic: Stereoselective epoxide arylation

# COMMUNICATION

*Ortho*-oxo substituted *trans* 2,3-diaryloxiranes were regio- and stereoselective arylated by aryl zinc reagents, obtained from the corresponding boronic acids by B-Zn exchange. The method allowed a direct and high yielding access to *trans* 2,3-diphenyl 2,3-dihydro benzofuran. The use of enantioenriched starting diaryl oxiranes resulted in no loss of stereochemical integrity in the final *trans* 2,3-dihydrobenzofuran

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