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A new regio- and stereoselective intermolecular Friedel–Crafts alkylation of phenolic substrates with aryl epoxides

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Abstract—A conceptually new regioselective and highly *syn*-stereoselective intermolecular Friedel–Crafts-type O-alkylation of phenols with aryl epoxides by the use of appropriately substituted aryl borates is reported. The carbon–carbon bond formation occurs in neutral and mild conditions without the need for external Lewis acids or transition metal catalysts.

1. Introduction

The functionalization of relatively unreactive arene C–H bonds with electrophiles is an area of current interest.[1] Although the Friedel–Crafts alkylation is one of the oldest and most intensively studied organic reactions, epoxides have rarely been used as the electrophilic partner.[2] *Strong Lewis* acids, such as Et_2AlCl, $SnCl_4$, BF_3–Et_2O, or protic additives, are often chosen for use with epoxides when the goal is an *intramolecular* addition to an alkene or aromatic systems, and several elegant biomimetic arene-epoxide cyclizations based on this concept have been reported.[3] On the other hand, *intermolecular* Friedel–Crafts alkylations of aromatics with epoxides have only sparingly been reported, and these reactions are often accompanied by various side reactions.[4] Often intractable mixtures of regioisomers have been obtained,[5] and only electron-rich nitrogen-based heterocycles, such as indoles, are able to react with epoxides in the presence of metal catalysts in a regioselective fashion.[6]

To the best of our knowledge, both intra- and intermolecular Friedel–Crafts reactions of aromatic compounds with epoxides invariably occur with *inversion of configuration* at the cleaved center. The regio- and stereoselective Friedel–Crafts alkylation of arenes with aromatic epoxides is particularly attractive both because aromatic epoxides are readily available in an enantioenriched form,[7] and because the product contains a benzylic carbon stereocenter.

Recently, we have reported a new *syn*-stereoselective ring opening of aryl epoxides and aziridines with aryl borates.[8] This reaction protocol allowed a smooth reaction of poorly nucleophilic phenols with three-membered heterocyclic rings in neutral condition to give phenoxy alcohols in a *syn*-stereoselective fashion (O-alkylation). For example, the reaction of styrene oxide with triphenylborate (**1a**, $R^1 = H$) afforded a good yield of the O-alkylated product **2a** along with a smaller amount (ca. 5%) of the corresponding *o*-(2-hydroxyalkyl) phenol **3a** deriving from an intermolecular Friedel–Crafts-type C-alkylation process (Scheme 1).

2. Results and discussion

We here report, a new cross-coupling reaction of aryl borates with aryl epoxides under mild and neutral conditions without the need for transition metal catalysts.

We reasoned that increasing the nucleophilic contribution of the attacking aromatic function might bring the C-alkylation process up to synthetically useful levels. For this purpose, arylborates **1a**–**j**, substituted in different position with groups having different electronic and steric properties were prepared and tested in our reaction conditions (Scheme 1).[9]

Keywords: Friedel–Crafts alkylation; Epoxides; Regioselectivity; Stereoselectivity.
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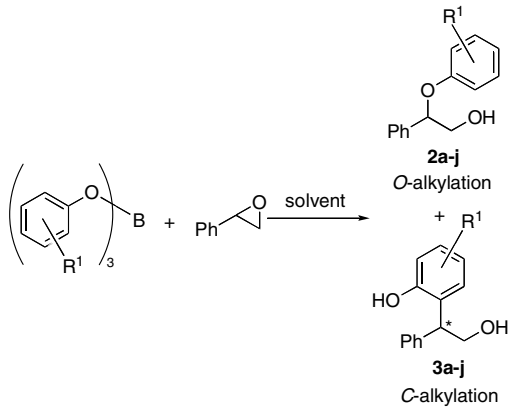


1a, R^1=H, **1b**, R^1=*o*-Me, **1c**, R^1=*o*-*t*-Bu, **1d**, R^1=*o*-TIPS, **1e**, R^1=*p*-OMe, **1f**, R^1=*p*-Me, **1g**, R^1=*m*-OMe, **1h**, R^1=2,3,5-tri-Me, **1i**, R^1=3,5-di-Me, **1j**, R^1=3,5-di-OMe.

Scheme 1. Product distribution of the reaction of a generic triarylborate with styrene oxide.

The use of borate **1b**, derived from *o*-cresol gave a modest but significant increase in the Friedel–Crafts type product **3b**, which was obtained as a single constitutional isomer in the *ortho*-position with respect to the phenolic oxygen (Table 1, entry 1).[10] The use of the more hindered tris-(*o*-*tert*-butyl phenyl)borate **1c** gave an almost equimolar mixture of products **3c** and **2c** deriving from C- and O-alkylation pathways, respectively (entry 2). As the nucleophilicity of the oxygen is most probably reduced by the presence of the *t*-butyl substituent, we also considered the use of more sterically hindered *o*-TIPS borate **1d**. The reaction of borate **1d** with styrene oxide was very fast, but the main reaction product was phenylacetaldehyde, derived from a rearrangement reaction of styrene oxide catalyzed by the Lewis acid (entry 3). The electron-donating mesomeric effect of the *p*-OMe substituent of borate **1e** increases the electron density of the oxygen atom,[11] whereas its inductive electron-withdrawing effect hampers the alkylation in the *ortho*-position of the phenol with respect to borate **1f**, which bears a methyl group and in which both effects go in the same sense (Table 1, cf. entries 4 and 5).

Interestingly, the reaction with borate **1f** can be carried out also at low temperatures with a slight increase in the C-alkylated product from 45% at rt to 58% at −78 °C (Table 1, entry 5). Consistently with our expectations, tris(*m*-methoxyphenyl)borate **1g** was able to activate both the *ortho*-position with respect to the phenolic oxygen by a mesomeric effect, and a substantial amount of the corresponding C-alkylated products **3g** and **3g′**, albeit as a ca. 3:1 mixture of regioisomers was obtained (Table 1, entry 6). The use of electron-rich substituted aryl borates **1h–j** gave a very fast reaction with (*R*)-(+)-styrene oxide even at low temperature with the obtainment in good yields of the corresponding C-alkylated products **3i–j** with a high *syn*-stereoselectivity and a complete regioselectivity (Table 1, entries 8–9).

To verify the scope of our new reaction protocol, some substituted aryl epoxides were examined (Table 2). The reactions of unsubstituted triphenylborate **1a** with *trans*-stilbene oxide and *trans*-glycidic ester **4**, afforded an increased amount of C-alkylated products (up to 27% of the crude mixture) with respect to the same reaction performed with styrene oxide (data not shown in Table 2). However, the use of the more electron-rich borates **1f**,**g**, and **1i** led to a significant but modest increase in the C-alkylation pathway pointing to the incursion of a more crowded transition state in the case of substituted epoxides (Table 2, entries 1–4). It is quite remarkable that these reactions gave the corresponding hydroxy phenols **5–8** with a complete *retention of configuration at the cleaved benzylic center*. Also *cis*-stilbene oxide gave substantial amounts of C-alkylated hydroxy phenol **9** with a good *syn*-stereoselectivity (Table 2, entry 5).[12]

Although our procedure often gives mixtures of products, it should be stressed that all C-alkylated products can easily be separated from the corresponding O-alkylated products and obtained in a pure state by simple chromatographic purifications.

The good to high *syn*-stereoselectivity observed throughout this work for C-alkylated products, as well

Table 1. Reaction of substituted arylborates **1b–j** with styrene oxide[a]

Entry	R^1 (borate)	Conditions	C-alk/O-alk[b]	Products [isolated yields (%)]
1	*o*-Me (**1b**)	2 h, rt	20/80	**3b/2b** (10/45)
2	*o*-*t*-Bu (**1c**)	6 h, rt	48/52	**3c/2c** (35/24)
3	*o*-TIPS (**1d**)	2 h, rt	70/30[c]	**3d/2d**[c]
4	*p*-OMe (**1e**)	1 h, rt	31/69	**3e/2e** (18/40)
5	*p*-Me (**1f**)	4 h, rt	45/55	
		12 h, −78 °C	58/42	**3f/2f** (48/32)
6	*m*-OMe (**1g**)	12 h, −78 °C	92/8[d]	**3g**+**3g′**/**2g** (35+11/4)
7	2,3,5-Tri-Me (**1h**)	1 h, −60 °C	87/13	**3h/2h** (67/nd)
8[e]	3,5-Di-Me (**1i**)	1.5 h, −78 °C	90/10	**3i/2i** (75/7)
9[e]	3,5-Di-OMe (**1j**)	1 h, −78 °C	>95/<5	**3j/2j** (77/nd)

[a] All reactions were carried out in accordance with the general procedure.[9]

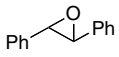
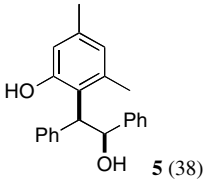
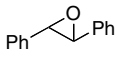
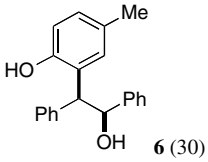
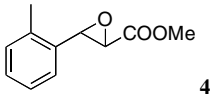
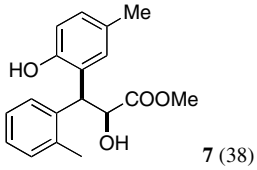
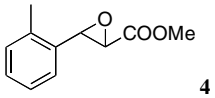
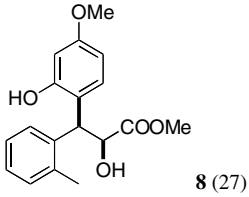
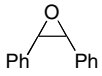
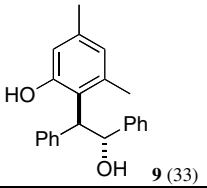
[b] Determined by ^{1}H NMR examination of the crude reaction mixture. Only the attack on the secondary benzylic position of the epoxide was observed.

[c] Phenyl acetaldehyde was the main product. See Supplementary data.

[d] Determined by HPLC. Two C-alkylated products were obtained in a 3:1 ratio (see Supplementary data for details).

[e] Performed with (*R*)-(+)-styrene oxide. Retention versus inversion configuration ratio was >92/8 in both cases, as determined by chiral HPLC analysis.

Table 2. Product distribution and stereoselectivity of the reaction of arylborates with substituted aromatic epoxides[a]

Entry	Epoxide	Conditions	Borate	C-alk/O-alk[b]	C-alkylated product[c]	*syn*/*anti*[d]
1		3 h, rt	R^1 = 3,5-Di-Me **1i**	40/60	 **5** (38)	>95/<5
2		18 h, rt	R^1 = *p*-Me **1f**	40/60	 **6** (30)	>95/<5
3	 **4**	4 h, rt	R^1 = *p*-Me **1f**	50/50	 **7** (38)	>95/<5
4	 **4**	4 h, −40 °C	R^1 = *m*-OMe **1g**	75/25[e]	 **8** (27)	>95/<5
5		3 h, rt	R^1 = 3,5-Di-Me **1i**	55/45	 **9** (33)	82/18

[a,b] See corresponding notes of Table 1.
[c] Isolated yields of the indicated C-alkylated product after chromatographic purification.
[d] Determined by ^{1}H NMR examination of the crude reaction mixture.
[e] See footnote d of Table 1.

for O-alkylated products[13] (Tables 1 and 2), points to an advanced carbocationic intermediate, such as **A** (Fig. 1). Nucleophilic attack would preferentially occur for entropic reasons by the *internal nucleophile*, with retention of configuration, to afford the corresponding *syn*-adducts (C-alkylated products from **B** and O-alkylated products from **C**), as experimentally found. In the intermolecular Friedel–Crafts alkylation, it is reasonable to hypothesize the formation of a chelated seven-membered transition state in which the new benzylic carbon–carbon bond is preferentially formed from the same side of the oxygen atom as the former epoxide ring (Fig. 1, path b).

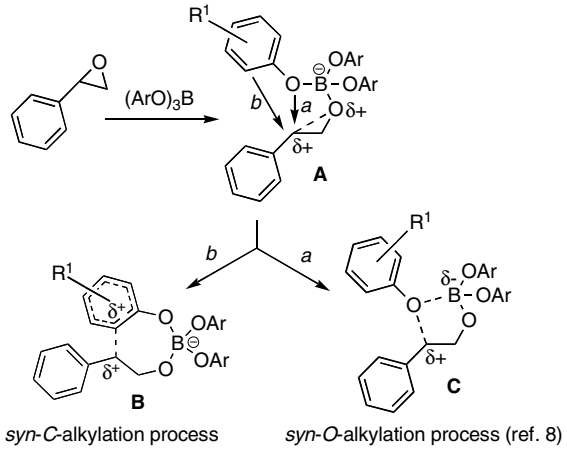


Figure 1. Competition between plausible chelated transition states of the *syn*-stereoselective pathways.

3. Conclusions

In summary, considering the importance of the stereoselective construction of benzylic carbon stereocenters, our new reaction protocol offers a simple route for stereodefined polyfunctional compounds, otherwise very difficult to obtain, in neutral conditions and without the need for transition metal catalysts.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.138.

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