Mild and Stereoselective Friedel–Crafts Alkylation of Phenol Derivatives with Vinyloxiranes: A New Access to Cycloalkenobenzofurans

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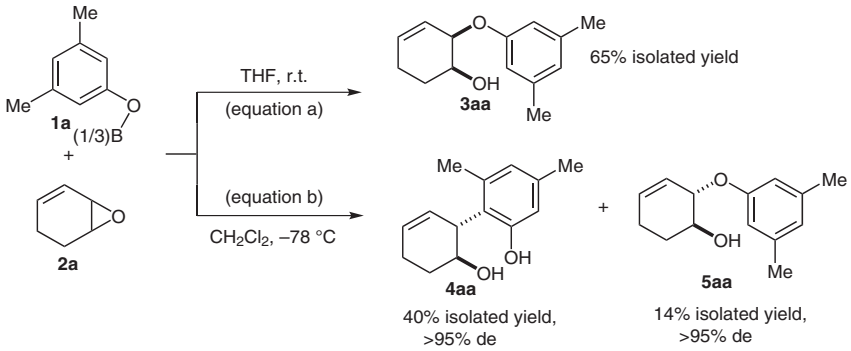
Abstract: The ring opening of vinyloxiranes with aryl borates under very mild and neutral conditions affords new hydroxyphenols with interesting levels of regio- and stereoselectivity. The subsequent Mitsunobu-type cyclodehydration proceeds with a good yield giving a new and easy access to cycloalkenobenzofurans.

Key words: Friedel–Crafts, vinyloxiranes, regioselectivity, stereoselectivity, fused-ring systems

Vinyloxiranes are a particular class of allylic electrophiles which are valuable building blocks for a variety of synthetic transformations.[1] Despite the abundance of studies on Friedel–Crafts alkylation,[2] vinyloxiranes have rarely been used as the electrophilic partner in intermolecular processes.[3] In these limited examples, strong Lewis acids were invariably used to promote the reaction and phenols have never been considered as the electrophilic partner.[4–6]

We report here a stereoselective intermolecular alkylation of electron-rich aryl borates with structurally different vinyloxiranes occurring under very mild reaction conditions. In connection with our recent study,[7] we took notice of the following: tris(3,5-dimethylphenyl)borate (**1a**) reacted readily at room temperature with 1,3-cyclohexadiene monoepoxide (**2a**) in THF to give *cis*-aryloxy alcohol **3aa** (O-alkylation pathway) as the only product, with high levels of *syn* stereoselectivity (>95% de) (Scheme 1, equation a), whereas upon switching the solvent to CH_2Cl_2, the reaction of borate **1a** with **2a** at –78 °C afforded *trans*-hydroxyphenol **4aa** and *trans*-aryloxy alcohol **5aa**, both with a high *anti* stereoselectivity (>95% de). The major product **4aa** was derived from a regioselective ring opening at the allylic position of the epoxide (S_N2-attack) by the *ortho* position of the phenol (C-alkylation pathway) (Scheme 1, equation b). Probably, the dramatically different reaction courses in the different solvents involve different mechanisms in which the nature of the cationic intermediate and solvation effects may account for many of the results. In the more solvating THF, the nucleophilic attack occurs by the internal nucleophile (i.e., the aryl borate tethered with the oxirane oxygen) with retention of configuration and with the prevalence of the 'harder' character of the oxygen of the phenol derivative.[8] On the other hand, the lesser solvating ability of the incipient allylic cationic intermediate by a low-polarity solvent such as CH_2Cl_2, may account for the normal ring opening with inversion of configuration by the highly nucleophilic arene **1a** at its 'softer' site (i.e., the *ortho* ring carbon of the phenol derivative).

Alternative reaction conditions were also considered. For example, the reactions of vinyloxirane **2a** with 4.5 equivalents of 3,5-dimethylphenol in CH_2Cl_2 at –78 °C in the presence of stoichiometric amounts of $BF_3{\cdot}Et_2O$ or catalytic amounts (5 mol%) of $In(OTf)_3$,[9] gave more complex reaction mixtures, in which *trans*-hydroxy ether **5aa** was the major reaction product.



Scheme 1 Product distribution in the reaction of aryl borate **1a** with vinyloxirane **2a** using different reaction conditions

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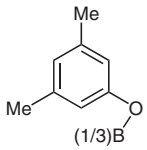
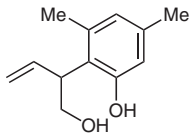
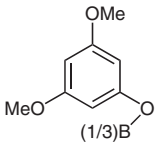
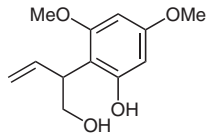
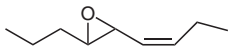
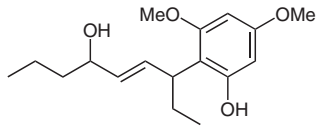
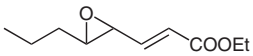
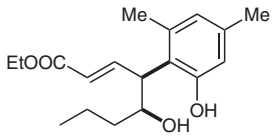
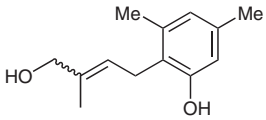
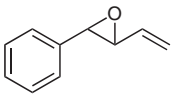
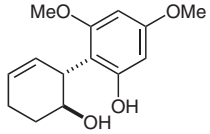
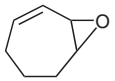
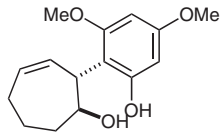
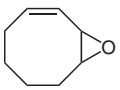
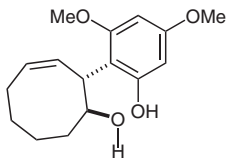
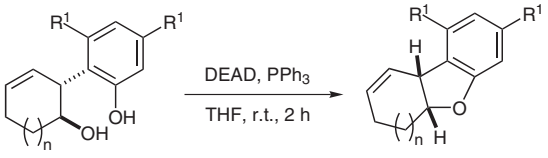
Table 1 Results of the Alkylation of Aromatic Borates **1a** and **1b** with Vinyloxiranes[a]

Entry	Vinyloxirane	Borate, conditions	Ratio C-/O-alkylation[b]	Ratio S_N2/S_N2'	Main product (Yield%)[c]	de[b]
1	 **6a**	 **1a**, –78 °C, 2 h	>95:<5	75:25[d]	 **6aa** (54)	n.a.
2	 **6a**	 **1b**, –78 °C, 2 h	>95:<5	82:18[d]	 **6ab** (75)	n.a.
3	 **6b**	**1b**, –78 °C, 2 h	>90:<10	<5:>95	 **6bb** (65)	n.d.
4	 **6c**	**1b**, –30 °C, 18 h	>95:<5	>95:<5	 **6cb** (40)	>95
5	 **6d**	**1a**, –78 °C, 18 h	88:12	15:85[d]	 **6da** (*E*/*Z* = 78:22) (48)	n.a.
6	 **6e**	**1b**, –78 °C, 1 h			Complex mixture	
7	 **2a**	**1b**, –78 °C, 18 h	>95:<5	>95:<5	 **4ab** (65)	>95
8	 **2b**	**1b**, –78 °C, 18 h	>95:<5	>95:<5	 **4bb** (58)	85
9	 **2c**	**1b**, –78 °C, 18 h	>95:<5	70:30	 **4cb** (35)[e]	>95

[a] All reactions were performed in accordance with the typical procedure.
[b] Diastereoisomeric excess was determined by ^1H and ^{13}C NMR analysis of the crude reaction mixture; n.d = not determined; n.a. = not applicable.
[c] Isolated yield of the pure product after chromatographic purification on silica gel, unless otherwise stated.
[d] The S_N2'-adducts were contaminated by substantial amounts (ca. 35% of the original crude mixture) of the corresponding *para*-alkylated S_N2 products.
[e] Obtained as an inseparable mixture with the corresponding S_N2'-adduct.

In order to verify the generality of the Friedel–Crafts-type ring opening of vinyloxiranes, the reactions of aryl borate **1a** and of tris(3,5-dimethoxyphenyl)borate (**1b**) with a series of aliphatic and cyclic vinyloxiranes in CH_2Cl_2 at a low temperature were examined (Table 1). Butadiene monoxide reacted readily with borates **1a** and **1b** to give fair isolated yields of the corresponding hydroxyphenols **6aa** and **6ab**, deriving from an S_N2 attack by the *ortho* position of the phenol derivative at the allylic position of the epoxide (entries 1 and 2, Table 1). A remarkable reversal of the regiocontrol of the ring opening was found in the reaction of (*Z*)-vinyloxirane **6b** with borate **1b**, affording the corresponding (*E*)-hydroxy phenol **6bb** deriving from an allylic transposition of the original double bond (S_N2'-attack) (entry 3). The substitution of the allylic residue with a carbomethoxy group, as present in compound **6c**, gave a diminished reactivity (75% conversion after 18 h at –30 °C), and restored the S_N2-type attack (entry 4). The reaction of a tertiary vinyloxirane, such as isoprene monoxide **6d**, with aryl borates **1a**,**b** proved to be less straightforward. For example, the reaction with borate **1a** gave low yields of diastereoisomeric hydroxyphenols deriving mainly from an S_N2'-attack (entry 5). Phenyl vinyloxirane **6e** invariably gave a complicated mixture of products (entry 6). To our delight, the reaction of borate **1b** with cyclic vinyloxiranes **2a–c** occurred exclusively with the C-alkylation manifold with complete regioselectivity at the allylic position of the epoxide and at the *ortho* position of the phenol derivative (entries 7 and 8). Only in the case of the eight-membered vinyloxirane **2c** substantial amounts (ca 30%) of the S_N2'-type-attack product were recovered as an inseparable mixture with the main product **4cb** (entry 9). Importantly, the stereoselectivity associated with the ring opening was uniformly high in all cases (entries 7–9, Table 1).

Several different methods are available for the obtainment of partially and fully hydrogenated dibenzofuran moieties, which are frequently found in biologically interesting molecules.[10] We envisioned that hydroxyphenols obtained from cyclic vinyloxiranes, could be suitable precursors to prepare cycloalkenobenzofurans of type **7** (Scheme 2). It should be noted that this class of compounds, bearing the double bond adjacent to the ring fusion and in β position with respect to the aromatic ring, is not easy to prepare by current methods.[11]



4aa,	R^1 = Me, n = 1	**7aa** (83%)
4ab,	R^1 = OMe, n = 1	**7ab** (81%)
4bb,	R^1 = OMe, n = 2	**7bb** (80%)
4cb,	R^1 = OMe, n = 3	**7cb** (70%)

Scheme 2 Mitsunobu-type cyclodehydration of cyclic hydroxyphenols to cycloalkenobenzofurans

The application of a Mitsunobu-type cyclodehydration to compounds **4aa** and **4ba**,[12] readily gave *cis*-3,4,4a,9b-tetrahydrodibenzofurans **7aa** and **7ba** (>95% de). Likewise, the cyclodehydration of hydroxyphenols **4bb** and **4cb** allowed a simple preparation of the corresponding new *cis*-benzofurans **7bb** and **7cb**, respectively, incorporating a seven- or an eight-membered ring bearing the double bond adjacent to the ring fusion and in the β-position with respect to the aromatic ring. The stereochemistry of the ring fusion was established by 1D NOESY experiments, thus unequivocally establishing the relative *trans* configuration of the starting cyclic hydroxyphenols of type **4** (Scheme 2).

To sum up, a mild ring opening of cyclic and aliphatic vinyloxiranes with representative electron-rich aryl borates afforded hydroxyphenols,[13] which are very difficult to access by other routes, with interesting levels of regio- and stereoselectivity. The subsequent cyclodehydration is of particular interest when cyclic hydroxyphenols are considered, because it gives a new and easy access to cycloalkenobenzofurans.

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References and Notes

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(13) Aryl borates **1a**,**b** were prepared from the corresponding commercially available phenols with $BH_3{\cdot}SMe_2$,[14] and were used immediately after their preparation.

Typical Procedure for the Preparation of Hydroxyphenols (Entry 7, Table 1): Under an argon atmosphere, a solution of aryl borate **1b** (705 mg, 1.5 mmol) in CH_2Cl_2 (1.0 mL) was added at –78 °C to a stirred solution of vinyloxirane **2a** (96 mg, 1.0 mmol) in CH_2Cl_2 (0.5 mL). The mixture was allowed to react for 18 h at –78 °C, then quenched with brine (2.0 mL) and diluted with Et_2O or CH_2Cl_2 (20 mL). Evaporation of the dried ($MgSO_4$) organic solution afforded a crude reaction mixture which was purified by silica gel column chromatography eluting with hexanes–EtOAc (7:3), to give pure 2-[(1*R**,6*S**)-6-hydroxycyclohexen-2-yl]-3,5-dimethoxyphenol (**4ab**; 162 mg, 65%), as a light yellow oil; TLC (hexanes–EtOAc, 1:1): R_f 0.36. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.70–1.90 (m, 1 H), 2.05–2.18 (m, 1 H), 2.30–2.43 (m, 2 H), 2.50–2.67 (br s, 1 H, CHO*H*), 3.82 (s, 3 H), 3.83 (s, 3 H), 3.95–4.10 (m, 2 H), 5.67–5.83 (m, 2 H), 5.93–6.05 (m, 1 H), 6.10–6.25 (m, 1 H), 6.50–6.70 (br s, 1 H, ArOH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 24.6, 30.7, 40.6, 55.1, 55.6, 71.2, 91.5, 94.5, 106.1, 107.7, 128.8, 156.9, 159.2, 159.9.

2-[(1*R,6*S**)-6-Hydroxycyclohexen-2-yl]-3,5-dimethylphenol (4aa)**: yield: 40%; solid; mp 119–122 °C; TLC (hexanes–EtOAc, 7:3): R_f 0.20. ^{1}H NMR (200 MHz, MeOD): δ = 1.56–1.86 (m, 2 H), 1.93–2.12 (m, 2 H), 2.17 (s, 3 H), 2.27 (s, 3 H), 3.62–3.89 (m, 1 H), 4.12–4.33 (m, 1 H), 5.45 (d, *J* = 9.8 Hz, 1 H), 5.56–5.71 (m, 1 H), 6.46 (s, 2 H). ^{13}C NMR (50 MHz, MeOD): δ = 21.0, 21.2, 26.4, 33.4, 45.3, 71.1, 115.3, 124.2, 125.4, 126.0, 131.7, 137.6, 139.5, 157.1.

2-(1-Hydroxybut-3-en-2-yl)-3,5-dimethylphenol (6aa): yield: 54%; colorless oil; TLC (hexanes–EtOAc, 6:4): R_f 0.31. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 2.28 (s, 3 H), 3.63 (br s, 1 H), 3.81–4.19 (m, 3 H), 5.04–5.24 (m, 2 H), 6.22 (ddd, J_1 = 16.6 Hz, J_2 = 10.4 Hz, J_3 = 5.3 Hz, 1 H), 6.58 (s, 1 H), 6.60 (s, 1 H), 8.26 (br s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.7, 44.8, 65.1, 116.1, 116.5, 122.4, 123.6, 136.0, 137.6, 154.7.

2-(1-Hydroxybut-3-en-2-yl)-3,5-dimethoxyphenol (6ab): yield: 75%; colorless oil; TLC (hexanes–EtOAc, 8:2): R_f 0.13. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.73 (s, 6 H), 3.89 (dd, J_1 = 10.2 Hz, J_1 = 3.2 Hz, 1 H), 4.02–4.15 (m, 1 H), 4.16–4.28 (m, 1 H), 5.00–5.19 (m, 2 H), 6.03–6.12 (m, 2 H), 6.13–6.23 (m, 1 H). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 40.0, 54.5, 55.7, 65.7, 91.2, 94.7, 108.0, 116.1, 136.7, 156.6, 158.6, 159.8.

(*E*)-2-(6-Hydroxynon-4-en-3-yl)-3,5-dimethoxyphenol (6bb): yield: 65%; colorless oil; TLC (hexanes–EtOAc, 7:3): R_f 0.27. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.79 (t, 3 H), 0.86 (t, *J* = 7.1 Hz, 3 H), 1.19–1.52 (m, 4 H), 1.62–1.82 (m, 2 H), 2.20 (br s, 1 H, CHO*H*), 3.69 (s, 3 H), 3.71 (s, 3 H), 3.74–3.89 (m, 1 H), 4.06–4.13 (m, 1 H), 5.55 (dd, J_1 = 16.3 Hz, J_2 = 6.7 Hz, 1 H), 5.98–6.18 (m, 3 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 12.3, 13.9, 18.61, 25.49, 38.27, 39.31, 55.1, 55.6, 72.7, 91.4, 94.4, 110.2, 132.6, 134.4, 158.8, 159.1.

(4*S,5*S**,*E*)-Ethyl 5-Hydroxy-4-(2-hydroxy-4,6-dimethylphenyl)oct-2-enoate (6cb)**: yield: 40%; colorless oil; TLC (hexanes–EtOAc, 7:3): R_f 0.19. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0. 93 (t, *J* = 7.1 Hz, 3 H), 1.25 (t, *J* = 5.7 Hz, 3 H), 1.33–1.74 (m, 4 H), 3.52 (br s, 1 H, CHO*H*), 3.74 (s, 6 H), 3.95–4.30 (m, 4 H), 5.78 (d, *J* = 15.8 Hz, 1 H), 6.04 (s, 1 H), 6.11 (s, 1 H), 7.38 (dd, J_1 = 15.8 Hz, J_2 = 7.2 Hz, 1 H), 9.22 (br s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.7, 14.1, 19.0, 38.1, 42.3, 55.1, 55.7, 60.3, 75.4, 91.0, 94.8, 108.0, 123.1, 145.2, 156.8, 158.2, 160.1, 167.0.

(1*S,2*R**)-2-(2-Hydroxy-4,6-dimethoxyphenyl)cyclohept-3-enol (4bb)**: yield: 58% [obtained as an inseparable mixture with 7% of the corresponding (1*S**,2*S**)-stereoisomer]; TLC (hexanes–EtOAc, 7:3): R_f 0.16. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.40–2.42 (m, 6 H), 3.70 (s, 3 H), 3.74 (s, 3 H), 3.93–4.17 (m, 2 H), 5.50–5.61 (m, 1 H), 5.77–5.95 (m, 1 H), 6.01 (d, *J* = 2.3 Hz, 1 H), (6.06 d, *J* = 2.3 Hz, 1 H), 6.94–7.03 (br s, 1 H, ArOH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.7, 27.8, 39.8, 43.3, 55.1, 55.6, 71.1, 91.2, 94.4, 109.0, 132.1, 133.0, 156.3, 159.5, 159.7.

Typical Procedure for the Preparation of 2,3-Dihydrobenzofuranes via Mitsunobu Cyclodehydration (Scheme 2): Triphenylphosphine (262.3 mg, 1.0 mmol) and diethylazodicarboxylate (118 μL, 0.75 mmol) were added to a stirred solution of hydroxyphenol **4ab** (125 mg, 0.5 mmol) in anhyd THF (2.0 mL) under argon. The reaction was followed by TLC up to complete consumption of the starting hydroxyphenol and the solvent was removed in vacuo. The crude reaction mixture was purified by silica gel column chromatography to give pure (4a*R**,9b*R**)-7,9-dimethoxy-3,4,4a,9b-tetrahydrodibenzo[*b*,*d*]furan (**7ab**; 94 mg, 81%) as a light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.75–2.31 (m, 4 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 3.81–3.88 (m, 1 H), 4.93–5.05 (m, 1 H), 5.73–5.95 (m, 2 H), 6.00 (d, *J* = 2.0 Hz, 1 H), 6.05 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.2, 25.1, 39.0, 55.1, 55.4, 82.3, 88.7, 91.0, 110.1, 126.0, 126.7, 156.7, 161.1, 161.5.

(4a*R,9b*R**)-7,9-Dimethyl-3,4,4a,9b-tetrahydrodibenzo[*b*,*d*]furan (7aa)**: yield: 83%; colorless oil; TLC (hexanes–Et_2O, 9:1): R_f 0.51. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.75–2.12 (m, 2 H), 2.19–2.30 (m, 2 H), 2.27 (s, 3 H), 2.30 (s, 3 H), 3.77 (br d, *J* = 6.9 Hz, 1 H), 4.94–5.00 (m, 1 H), 5.68–5.95 (m, 2 H), 6.48 (s, 1 H), 6.50 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.3, 19.0, 21.4, 24.9, 40.1, 81.3, 108.0, 122.6, 125.1, 126.9, 127.8, 134.0, 138.2.

(5a*R,10a*R**)-1,3-Dimethoxy-6,7,8,10a-tetrahydro-5a*H*-benzo[*d*]cyclohepta[*b*]furan (7bb)**: yield: 80% (obtained as an inseparable mixture with 10% of the corresponding *trans* stereoisomer); light yellow oil; TLC (hexanes–EtOAc,

9:1): R_f 0.38. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.55–1.75 (m, 2 H), 1.92–2.07 (m, 2 H), 2.09–2.22 (m, 2 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 4.25 (d, J = 9.8 Hz, 1 H), 4.88 (ddd, J_1 = 4.5 Hz, J_2 = 9.8 Hz, 1 H), 5.62–5.68 (m, 2 H), 6.00–6.05 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.4, 26.7, 28.7, 42.4, 55.3, 55.5, 85.5, 88.1, 91.1, 127.6, 129.7, 159.0, 160.3, 160.7.

(5a*S,11a*S**,*Z*)-1,3-Dimethoxy-5a,6,7,8,11a-hexahydrobenzo[*b*]cycloocta[*d*]furan (7cb)**: yield: (70%); light yellow oil; TLC (hexanes–EtOAc, 9:1): R_f 0.45. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95–2.25 (m, 8 H), 3.72 (s, 3 H), 3.76 (s, 3 H), 4.10–4.26 (m, 1 H), 4.50–4.67 (m, 1 H), 5.11 (dd, J_1 = 10.6 Hz, J_2 = 7.0 Hz, 1 H), 5.68–5.88 (m, 1 H), 6.00 (s, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.6, 26.7, 28.2, 29.2, 40.4, 55.5 (2 × C), 88.3, 91.3, 91.5, 11.8, 130.5, 133.3, 156.7, 160.5, 161.6.

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