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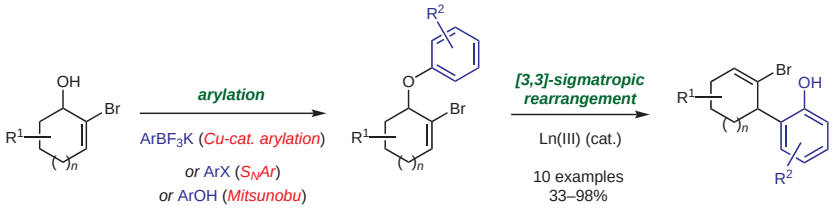
# Sequential O-Arylation/Lanthanide(III)-Catalyzed [3,3]-Sigmatropic Rearrangement of Bromo-Substituted Allylic Alcohols

**Timothy R. Ramadhar**
**Jun-ichi Kawakami**
**Robert A. Batey***

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George St., Toronto, ON, M5S 3H6, Canada
rbatey@chem.utoronto.ca

Dedicated to the Cardinal Chemist, the inimitable Prof. Victor Snieckus, on the occasion of his 80th birthday

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**Abstract** Lanthanide(III)-catalyzed aryl-Claisen rearrangement of substrates bearing halo-substituted allyl groups, specifically 2-bromoallyl aryl ethers, afford *ortho*-2-bromoallylphenols. Aryl ether substrates were synthesized from brominated allylic alcohols via Mitsunobu reaction, Cu(II)-catalyzed arylation using potassium aryltrifluoroborate salts, or $S_NAr$ reaction. Aryl-Claisen rearrangements proceeded in moderate to excellent yields using Eu(III) catalysis. The alkenylbromide functionality remains intact, illustrating the compatibility of synthetically important alkenylhalides during C–O/C–C σ-bond migration processes. Subsequent derivatization of the *ortho*-2-bromoallylphenol products through O-alkylation or C-arylation/alkenylation via Suzuki–Miyaura cross-coupling demonstrate the potential to access densely-functionalized molecules.

**Key words** aryl-Claisen [3,3]-sigmatropic rearrangement, alkenylbromide, arylation, organotrifluoroborate salt, lanthanide catalysis, phenols, Suzuki–Miyaura reaction, Chan–Lam–Evans arylation

Alkenylhalides are important functional groups in synthesis since they serve as site-specific groups to introduce C–C, C–N, C–O, or C–S bonds through substitution.[1] These transformations are most commonly achieved through metal-catalyzed transformations, typically through Pd catalysis, such as Suzuki–Miyaura, Stille, Sonogashira, Heck, and carbonylation reactions.[2] The alkenylhalide functionality can also be reduced to alkenes, participate in E2 elimination to generate alkynes, or can be transformed with either strongly reducing metals or undergo metal–halogen exchange to form organometallic reagents such as alkenyl Grignard, alkenyllithium, or alkenylzinc reagents.[3]

In view of the importance of this functionality in organic synthesis, developing strategies and reaction conditions that are compatible with the alkenylhalide functional group is of significant interest. As part of a wider program in the use of pericyclic transformations,[4] we have become interested in establishing methods that allow access to alkenylhalides, particularly cyclic variants, using sigmatropic rearrangement, cycloaddition, and electrocyclic reactions. The aryl-Claisen sigmatropic rearrangement reaction is a well-established method for the formation of *ortho*-substituted phenols.[5] Herein, we demonstrate the feasibility of aryl-Claisen rearrangements of 2-bromoallyl aryl ethers to give *ortho*-2-bromoallylphenols using Eu(III) catalysis.

To evaluate the feasibility of combining O-arylation with lanthanide(III)-catalyzed [3,3]-sigmatropic rearrangements on halogenated substrates, 2-bromo-substituted allylic frameworks were chosen. An overall strategy for the formation of halo (bromo)-allylsubstituted phenol **3** was envisaged utilizing a sequential arylation/aryl Claisen rearrangement of allylic alcohol **1** via aryl allylic ether **2** (Scheme 1). Requisite bromo-substituted precursors **1** are accessible through various methods, including electrocyclic ring opening/solvolysis of dibromocyclopropanes[6] and bromination/Luche reduction of enones. The alkenylbromide functionality in *ortho*-2-bromoallylphenol product **3** can be further reacted through reduction, C–H bond functionalization, or cross-coupling to **4**. Alternatively, conversion of the phenol group through O-alkylation or arylation would provide a route to ether **5**, the C–X bond of which could be utilized for further functionalization or C–M bond formation (e.g., C–Li, C–MgX, C–ZnX).

For allyl aryl ether **2** formation, there are numerous methods for O-arylation of **1**, but not all would be compatible with the C–X functionality, such as Pd(0)-catalyzed Buchwald–Hartwig O-arylation.[7] While the presence of the alkenylhalide functionality is problematic for Pd(0)-catalyzed reactions, copper-catalyzed arylations using boronic acids (the Chan–Lam–Evans O-arylation reaction),[8] or the corresponding aryltrifluoroborate variant,[9] would likely not be affected. Alternatively, coupling of the allylic alcohol **1**

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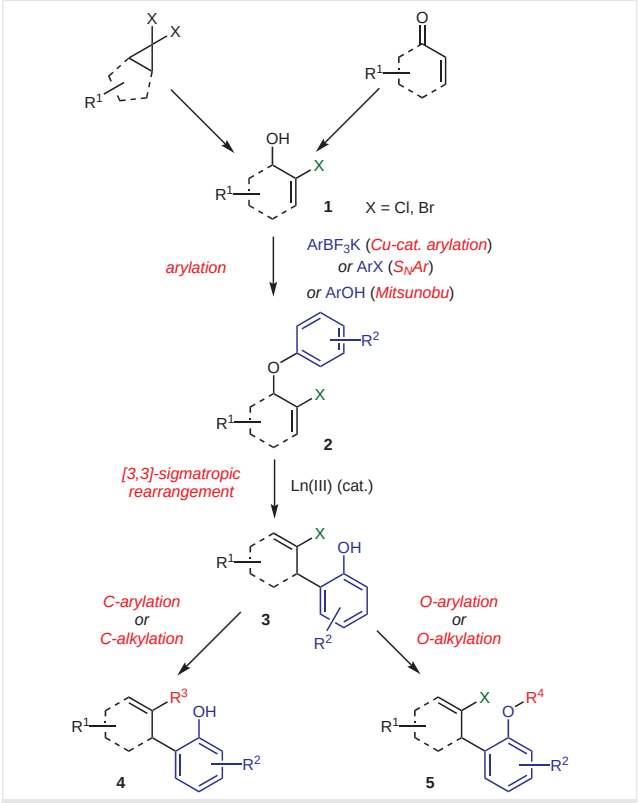
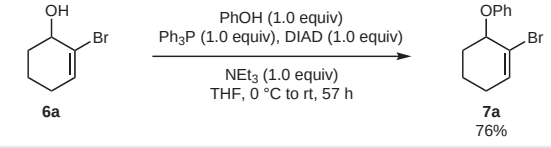



**Scheme 1** Sequential O-arylation, [3,3]-sigmatropic rearrangement strategy for the synthesis of functionalized alkenylhalides **3**

with phenols using the Mitsunobu reaction[10] or with electron-deficient aryl rings under nucleophilic aromatic substitution ($S_NAr$) conditions[11] would also provide access to **2**.[12]

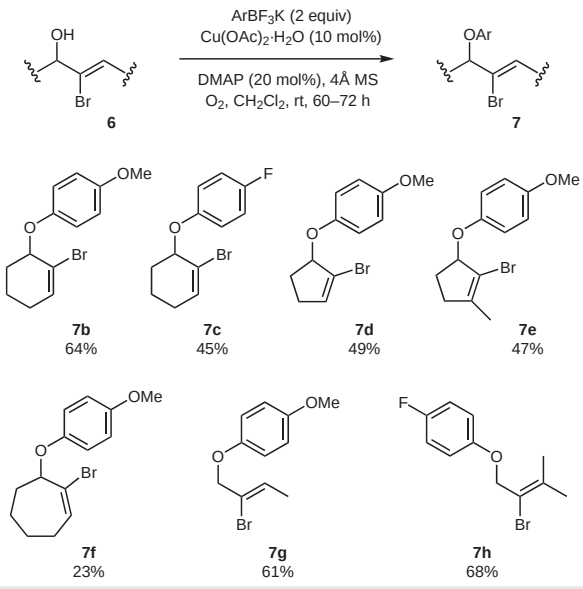
Encouraged by our success in using Eu(fod)$_3$ for the domino aryl-Claisen rearrangement of bisaryl ethers to afford contiguous bisphenols,[13] we envisaged performing the aryl-Claisen [3,3]-sigmatropic rearrangement on aryl ether **2**, using Ln(III) catalysis.[14] This method, which was originally reported by Trost,[15] uses the inexpensive oxophilic Eu(fod)$_3$ (fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate) catalyst, allows for stereospecific and highly stereoselective aryl transposition through a suprafacial migration manifold (as opposed to racemization via a formal ionic mechanism, as observed by Trost for the aryl-Claisen rearrangement on enantiopure substrates with $BCl_3$, $Et_2AlCl$, and lanthanide(III) triflate additives),[15] and avoids the use of very high temperatures that are usually required for aryl-Claisen reactions (previous examples of rearrangement of simple 2-bromoallyl aryl ethers have required heating at 200 °C).[16]

For introduction of a phenyl ether, a Mitsunobu-based nucleophilic arylation of **6a** using PhOH was found to be the most convenient method for O-phenylation, affording **7a** in 76% yield (Equation 1).




**Equation 1** Substrate synthesis via a nucleophilic (Mitsunobu) arylation route

More electron-rich aryl groups were introduced on brominated cyclic and acyclic allylic primary and secondary alcohols using a mild Cu(II)-catalyzed O-arylation reaction with aryltrifluoroborate coupling partners (Scheme 2).[17] We have previously demonstrated the advantage of using aryltrifluoroborate salts rather than arylboronic acids for the arylation of aliphatic alcohols using copper catalysis.[9] Formation of five- and six-membered cycloalkenyl arylation products **7b–e** occurred in moderate yields, while reaction of 2-bromocyclohep-2-en-1-ol occurred in poorer yield (23%, **7f**). Linear substrates bearing primary allylic alcohols and trisubstituted or tetrasubstituted bromoalkenes were O-arylated in 61% (**7g**) and 68% (**7h**) yields, respectively.




**Scheme 2** Synthesis of *O*-aryl 2-bromoallylic ether substrates **7** through Cu(II)-catalyzed oxidative coupling of **6** with aryltrifluoroborate salts

More electron-deficient aryl groups were introduced using an $S_NAr$ arylation strategy. Thus, nitroaryl-substituted products were formed through $S_NAr$ reaction of **6a** with either 2- or 4-nitrofluorobenzene, producing **7i** and **7j** in excellent yields, while $S_NAr$ reaction of (*Z*)-2-bromobut-2-en-1-ol with 2-nitrofluorobenzene afforded **7k** in 59% yield (Scheme 3). In addition to their application in aryl-Claisen



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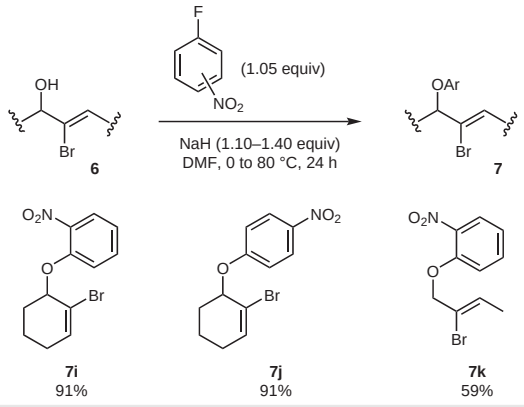
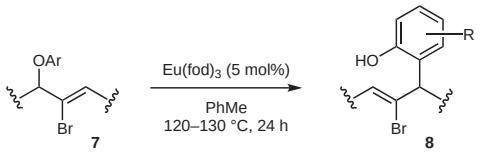
rearrangements, C–Br bond in the products **7** can be utilized for further transformations, such as C–H functionalization to give benzofurans.[12]




**Scheme 3** Synthesis of *O*-aryl 2-bromoallylic ether substrates through $S_NAr$ substitution

Next, the *O*-aryl 2-bromoallylic ether substrates **7** were subjected to aryl-Claisen rearrangement reaction (Table 1).[18] The reaction conditions were derived from a prior report in our laboratory describing $Eu(fod)_3$-catalyzed domino aryl-Claisen rearrangements;[13] thus, *O*-aryl 2-bromoallylic ether substrates **7** were reacted with 5 mol% of $Eu(fod)_3$ in toluene at 120–130 °C in a sealed tube for 24 hours. Reactions on *O*-aryl 2-bromocyclohexenyl ether substrates typically occurred to give the *ortho*-substituted phenols **8a–c** in excellent yields (82–98%). The reaction was also successful for cyclopentenyl and cycloheptenyl substrates (**7d** and **7f**, respectively). However, when cyclopentenyl substrate **7e** bearing a tetrasubstituted alkene was subjected to $Eu(fod)_3$ catalysis, product **8e** was not detected, and decomposition was observed. The aryl-Claisen reactions of linear *O*-aryl 2-bromoallylic ether substrates were also successful. Reaction of **7g** furnished **8g** in excellent yield (94%), illustrating that rearrangement occurs with allylic transposition under Ln(III) conditions (cf. the use of $Et_2AlCl$). Similarly, the aryl-Claisen rearrangement of the more sterically hindered **7h** furnished **8h**, albeit in only 33% yield. Tripling the catalyst loading only afforded a 39% yield. A lower yield was also observed for the reaction of **7j** (49%, **8j**), which incorporates a *para*-$NO_2$ group. Presumably the nitro group lowers the Lewis basicity of the ethereal oxygen and diminishes its propensity to directly interact with $Eu(fod)_3$. However, with the nitro group located at the *ortho* position (**7i**), the product yield increased to 98% (**8i**). It is unclear why the yield for the rearrangement of **7i** was high; however, we speculate that the proximal nitro group may aid in directing the catalyst to the ethereal oxygen. Rearrangement of **7k** occurred sluggishly; however, by tripling the catalyst loading (15 mol%) and doubling the reaction time (48 h), phenol **8k** was afforded in 89% yield (compared to 65% yield if 5 mol% of $Eu(fod)_3$ was used for 24 h). Overall, the alkenyl bromide functionality is compatible with the $Eu(fod)_3$-catalyzed aryl-Claisen reaction conditions and thus is available for further derivatization.

**Table 1** $Eu(fod)_3$-Catalyzed Aryl-Claisen Rearrangements of *O*-Aryl 2-Bromoallylic Ether Substrates **7**



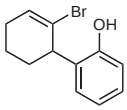
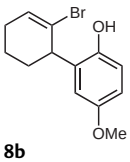
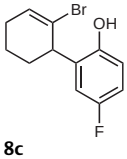
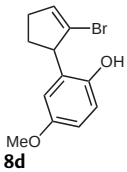
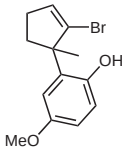
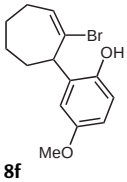

| Entry | Substrate | Product | Yield (%)[a] |
|---|---|---|---|
| 1 | **7a** |  **8a** | 82 |
| 2 | **7b** |  **8b** | 82 |
| 3 | **7c** |  **8c** | 96 |
| 4 | **7d** |  **8d** | 85 |
| 5 | **7e** |  **8e** | not observed |
| 6 | **7f** |  **8f** | 93 |

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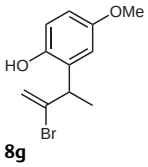
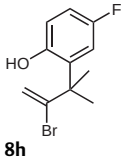
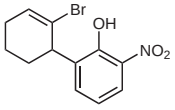
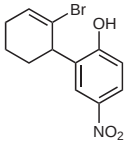
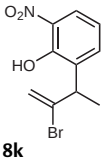
Table 1 (continued)

| Entry | Substrate | Product | Yield (%)[a] |
|---|---|---|---|
| 7 | **7g** |  **8g** | 94 |
| 8 | **7h** |  **8h** | 33<br>39[b] |
| 9 | **7i** |  **8i** | 98 |
| 10 | **7j** |  **8j** | 49 |
| 11 | **7k** |  **8k** | 65<br>89[c] |

[a] Isolated yield following column chromatography.
[b] 15 mol% $Eu(fod)_3$ was used.
[c] 15 mol% $Eu(fod)_3$ and 48 h reaction time was used.

X-ray quality crystals of racemic **8b** were grown through slow evaporation from $CDCl_3$. The X-ray crystal structure, solved and refined in the centrosymmetric monoclinic $P2_1/c$ space group, depicts the expected atom connectivities and thus validates the sequential Cu(II)-catalyzed arylation/aryl-Claisen rearrangement reaction for these systems (Figure 1).[19]

Following the successful demonstration of aryl-Claisen rearrangements on *O*-aryl 2-bromoallylic ether substrates, we aimed to determine the potential of further elaboration of the alkenylbromide functionality. Proof-of-concept for alkenylbromide utilization was established through Suzuki–Miyaura cross-coupling reaction between **8a** and potassium vinyltrifluoroborate, using slightly modified conditions to those reported by Molander,[20] to furnish **9** (Scheme 4). However, an attempt to perform a Suzuki–Miyaura reaction on the same substrate with phenylboronic acid and the electron-rich DavePhos phosphine ligand[21] failed; only starting material was observed.

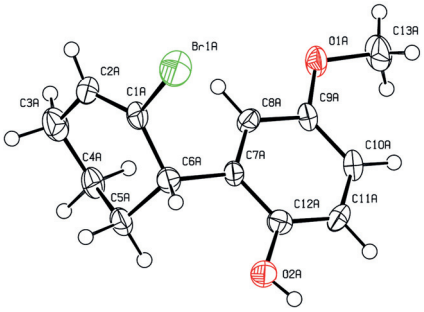
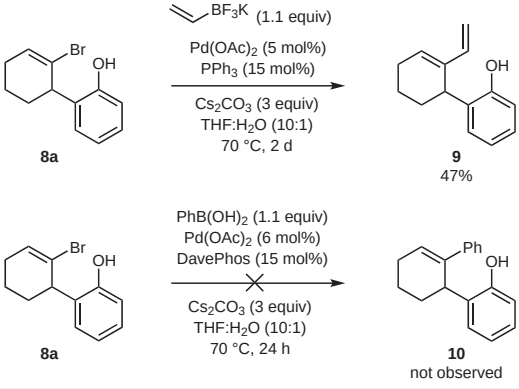



**Figure 1** X-ray crystal structure of **8b** (ellipsoids are shown at 50% probability level, and only one of two molecules in the asymmetric unit is shown)




**Scheme 4** Suzuki–Miyaura cross-coupling reactions of alkenyl bromide **8a** bearing an unprotected phenol hydroxyl group

Speculating that the free phenolic hydroxyl group might be problematic for some cross-coupling reactions, we sought to test the aforementioned failed Suzuki–Miyaura reaction on a substrate with a protected phenolic hydroxyl group (Scheme 5). Compound **8b** was first *tert*-butyl-protected with $Boc_2O$ under Sc(III)-catalyzed conditions[22] to afford **11** in 80% yield. Initial attempts to perform cross-coupling reactions with **11** failed, presumably on account of the steric bulk imparted by the *tert*-butyl group, and only starting material was observed. Therefore, we attempted another route where **8a** was methylated using dimethylsulfate to generate **12** in excellent yield (90%). Repeating the Suzuki–Miyaura cross-coupling conditions on **12** with phenylboronic acid and DavePhos afforded bisaryl-substituted compound **13** in 80% yield. Therefore, phenol O-alkylation using an alkylating group of low steric bulk is a viable strategy to remedy situations where cross-coupling reactions fail with unprotected alkenyl bromide phenol substrates.

In summary, sequential O-arylation/Ln(III)-catalyzed aryl-Claisen rearrangement on allylic alcohols bearing a participatory alkenylbromide functionality is demonstrated to afford *ortho*-2-bromoallylphenols. The alkenylbromide

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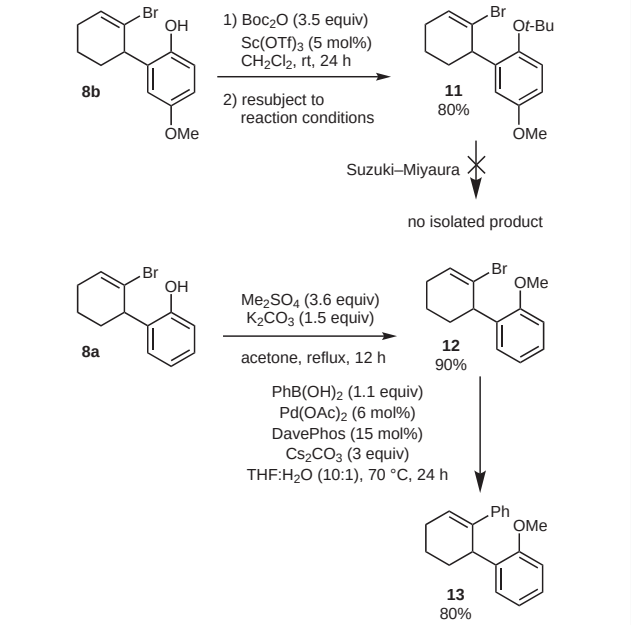


**Scheme 5** O-Alkylation of **8b** and **8a** to ethers **11** and **12** and the subsequent Suzuki–Miyaura cross-coupling reaction of **12**

functionality is compatible with several O-arylation processes (via Cu(II)-catalysis, Mitsunobu, and $S_NAr$) and Eu(III)-catalyzed aryl-Claisen [3,3]-sigmatropic rearrangements. The alkenylbromide functionality can be further elaborated through Suzuki–Miyaura cross-coupling reactions. Overall, this two-step, sequential strategy readily provides access to densely-functionalized polycyclic scaffolds. Further studies involving applications towards total synthesis and for the construction of polycyclic systems bearing axial chirality can be envisaged.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590890.

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(17) **General Procedure for O-Aryl 2-Bromoallylic Ether Synthesis via Cu(II)-Catalyzed Arylation**

A suspension of $ArBF_3K$, $Cu(OAc)_2{\cdot}H_2O$ (10 mol%), DMAP (20 mol%), and powdered 4Å MS in $CH_2Cl_2$ was stirred at rt for 5 min. To this suspension was added alcohol **6**. The mixture was stirred at rt for 60–72 h under an $O_2$ atmosphere. Subsequently, the mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The resultant crude mixture was purified using flash column chromatography on silica gel to afford aryl ether **7**.

**Example**

Reaction of **6a** (0.250 g, 1.4 mmol) with $4\text{-}FC_6H_4BF_3K$ (0.601 g (95% purity), 2.8 mmol) using the general procedure afforded **7c** (0.171 g, 45%) as a clear oil.

**Analytical Data for Compound 7c**

$R_f$ = 0.43 (5% EtOAc/hexanes). IR (thin film): $\nu_{max}$ = 3073, 3051, 2945, 2934, 2866, 2834, 1647, 1601, 1505, 1439, 1368, 1240, 1202, 1090, 1057, 999, 974, 914, 826, 785, 725 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.00–6.94 (4 H, m), 6.38 (1 H, dd, *J* = 5.0, 3.0 Hz), 4.64–4.62 (1 H, m), 2.27–2.19 (1 H, m), 2.14–2.04 (1 H, m), 1.86–1.74 (2 H, m), 1.70–1.61 (1 H, m). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 158.0 (d, $^1J_{CF}$ = 239.5 Hz), 154.4 (d, $^4J_{CF}$ = 2.5 Hz), 135.0, 121.2, 118.6 (d, $^3J_{CF}$ = 8.0 Hz), 116.1 (d, $^2J_{CF}$ = 23.0 Hz), 78.0, 29.3, 28.0, 16.8. $^{19}F$ NMR (376 MHz, $CDCl_3$): δ = –123.41 (m). LRMS ($EI^+$): *m/z* (rel. intensity) = 272 (5), 270 (5) $[M]^+$, 161 (14), 160 (93), 159 (17), 158 (94), 112 (78), 79 (100). HRMS ($EI^+$): *m/z* calcd for $C_{12}H_{12}OFBr$ $[M]^+$: 270.0056; found: 270.0061.

(18) **General Procedure for the Aryl-Claisen Rearrangement of *O*-Aryl 2-Bromoallylic Ethers 7 to 8**

A mixture of aryl ether **7** and $Eu(fod)_3$ (5 mol%) in PhMe was stirred at 120–130 °C in a sealed tube for 24 h under an atmosphere of argon. The mixture was directly purified (without removal of the solvent under reduced pressure) by flash column chromatography on silica gel (gradient: hexanes – 25% EtOAc/hexanes) to afford phenol **8**.

**Example**

Reaction of **7c** (0.050 g, 0.18 mmol) using the general procedure afforded **8c** (0.048 g, 96%) as a white solid.

**Data for Compound 8c**

Mp 52–53 °C (EtOAc/hexanes); $R_f$ = 0.53 (25% EtOAc/hexanes). IR (thin film with $CDCl_3$): $\nu_{max}$ = 3468 (br), 2928, 2860, 1644, 1620, 1597, 1504, 1434, 1332, 1260, 1172 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 6.89 (1 H, dd, *J* = 9.5, 3.0 Hz), 6.82 (1 H, ddd, *J* = 8.5, 8.0, 3.0 Hz), 6.70 (1 H, dd, *J* = 8.5, 4.5 Hz), 6.40 (1 H, ddd, *J* = 4.0, 4.0, 1.5 Hz), 4.81 (1 H, br s), 4.02–3.99 (1 H, m), 2.26–2.13 (2 H, m), 2.11–2.03 (1 H, m), 1.90–1.83 (1 H, m), 1.63–1.52 (2 H, m). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 157.4 (d, $^1J_{CF}$ = 237.5 Hz), 149.3 (d, $^4J_{CF}$ = 2.5 Hz), 133.2, 131.0 (d, $^3J_{CF}$ = 6.5 Hz), 123.5, 116.6 (d, $^3J_{CF}$ = 8.0 Hz), 116.4 (d, $^2J_{CF}$ = 24.0 Hz), 114.1 (d, $^2J_{CF}$ = 23.0 Hz), 44.0, 31.1, 27.9, 18.0. $^{19}F$ NMR (376 MHz, $CDCl_3$): δ = –123.9 (ddd, $J_{FH}$ = 8.5, 8.5, 4.5 Hz). LRMS ($EI^+$): *m/z* (rel. intensity) = 272 (5), 270 (6) $[M]^+$, 191 (39), 163 (29), 149 (16), 133 (11), 125 (13), 109 (10), 86 (73), 84 (100). HRMS ($EI^+$): *m/z* calcd for $C_{12}H_{12}OBrF$ $[M]^+$: 270.0056; found: 270.0059.

(19) CCDC 1558909 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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