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# Enantioselective Aromatic Claisen Rearrangement

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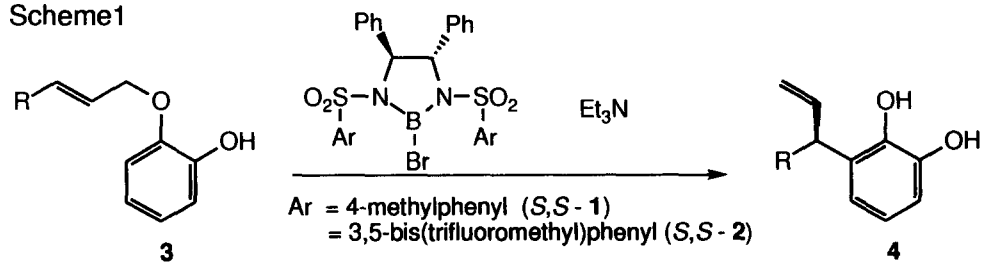
**Abstract:** The development of a highly enantioselective aromatic Claisen rearrangement was achieved by the reaction of catechol mono allylic ethers with chiral boron reagent **1**. This system was also shown to avoid the formation of para rearrangement and abnormal Claisen rearrangement products. © 1997 Elsevier Science Ltd.

Claisen rearrangement has attracted much attention as an attractive tool for the construction of new carbon-carbon bonds.[1] In the Claisen rearrangement, the control of the newly formed chiral center is very important and an enantioselective construction of the chiral center by using an achiral substrate is a challenging theme in organic synthesis. Approaches for development of enantioselective Claisen rearrangement have been examined by several groups. Although successful enantioselective *aliphatic Claisen rearrangements* of achiral substrates were reported by Yamamoto *et al.*,[2] Corey *et al.*,[3] and Kazmaier *et al.*,[4] enantioselective *aromatic Claisen rearrangement* has not been reported. There would be several problems to be solved in enantioselective aromatic Claisen rearrangement of an achiral substrate (2-alkenyl aryl ethers such as **3**); that is, an efficient reaction system should be established to achieve 1) high enantioselectivity on the newly formed chiral center, 2) complete regioselectivity (ortho selectivity), and 3) suppression of the formation of a byproduct through the abnormal Claisen rearrangement.[5] We report herein the highly enantioselective and regioselective aromatic Claisen rearrangement which avoids the formation of an abnormal Claisen product by using catechol mono allylic ether derivatives **3** and chiral boron reagent **1**.

Scheme1

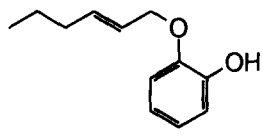
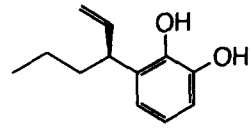
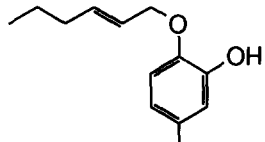
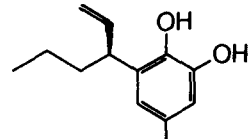
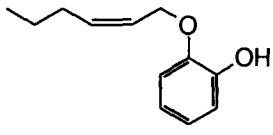
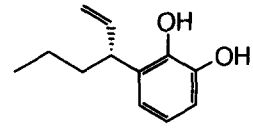
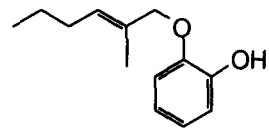
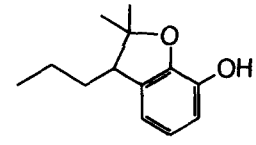
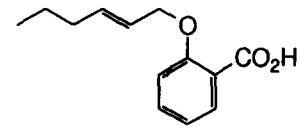
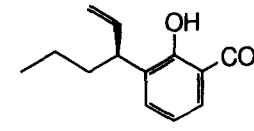



**3** **4**

As the substrate for aromatic Claisen rearrangement was chosen catechol mono allylic ether derivatives **3**[6] which have a hand to form a σ-bond with a chiral boron reagent. In our hypothesis, the formation of a σ-bond between the phenolic hydroxyl group and the boron complex would not bring about significant decrease in Lewis acidity of the boron atom. Thereby, the allylic oxygen coordinates to the boron atom to form a five-

membered cyclic complex. Furthermore, by forming this cyclic intermediate, facially selective shielding of the aromatic ring would preferentially occur on one site by the chiral ligand leading to enantioselective rearrangement (see Figure 1).

**Table 1. Enantioselective aromatic Claisen rearrangement**

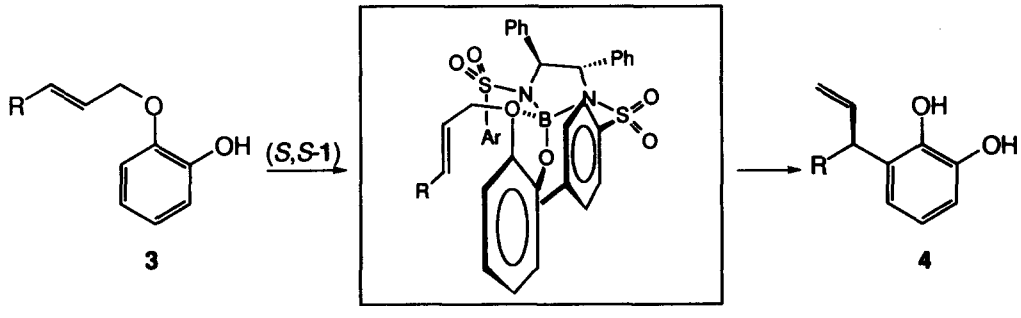
| Entry | Substrate | Ligand | Temp. | Time | Product | Yield (%)[a] | ee (%) |
|---|---|---|---|---|---|---|---|
| 1 |  **3a** | 1 | -45 °C | 4 d |  **4a** | 89 | 94[b] |
| 2 | **3a** | 2 | -45 °C | 24 h | **4a** | 88 | 88[b] |
| 3 |  **3b** | 1 | -45 °C | 3 d |  **4b** | 97 | 93[c] |
| 4 |  **3c** | 1 | -23 °C | 2 d |  **4c** | 92 | 95[b] |
| 5 |  **3d** | 1 | -45 °C | 27 h |  **5** | 80 | 86[d,e] |
| 6 |  **6** | 1 | -45 °C | 24 h |  **7** | 51 | 57[f] |

[a] Isolated yield. [b] Optical purity was determined by HPLC using chiralcel OK column after derivatized to dimethyl ether. [c] Optical purity was determined by 300 MHz $^1$H NMR spectrum after derivatized to MTPA ester. [d] Optical purity was determined by HPLC using chiralcel AD column. [e] Stereochemistry was not determined. [f] Optical purity was determined by HPLC using chiralcel OK column after derivatized to methyl ester.

Claisen rearrangement of substrate **3a** catalyzed by the *in situ* generated 1.5 equivalent of chiral boron reagent **1**[3] proceeded smoothly in the presence of triethylamine (1.5 eq.) at -45 ℃ in dichloromethane to give ortho substituted catechol derivative **4a**[7] of 94 % ee in 89 % yield (Table 1, entry 1). The products formed by rearrangement of the allylic moiety to para position and by abnormal Claisen rearrangement could not be detected.[8] Other amines (pyridine and diisopropylethylamine) also worked as well as triethylamine. In the use of ligand **2**, the reaction proceeded much faster than with ligand **1**, but the enantioselectivity slightly decreased (entry 2). These results may indicate that the increase in Lewis acidity of the boron atom enhances the reaction rate, but the steric repulsion on both faces of the benzene ring of the substrate **3a** will be developed at the same time by increasing the steric size of the aromatic sulfonamide moiety from 4-methylphenyl in **1** to 3,5-bis(trifluoromethyl)phenyl in **2**. The rearrangement of substrate **3b** also proceeded to give product **4b** in high selectivities (entry 3). The rearrangement of substrate **3c** which has a (*Z*)-allylic moiety needed higher reaction temperature than in the case of (*E*)-allylic derivatives to give **4c** (95 % ee, 92 % yield), an enantiomer of product **4a** (entry 4). In the case of trisubstituted allylic ether derivative **3d**, benzofuran derivative **5** was obtained through the Claisen rearrangement and subsequent acid-mediated cyclization during the workup step (entry 5). Under the reaction conditions as above, the Claisen rearrangement of 2-hexenyl phenyl ether and *O*-methyl protected catechol mono allylic ethers, both of which have no hydroxyl group at the ortho position, did not proceed. These results indicate that B-O bond formation between the chiral boron reagent and the hydroxyl group at the ortho position of the substrate is crucial for the Claisen rearrangement to proceed.[9] We also examined the Claisen rearrangement of substrate **6**, which may form a six-membered cyclic intermediate. In this case, both enantioselectivity and the chemical yield of the ortho-rearranged product **7** (57 % ee, 51 % yield) were moderate along with the formation of the para-rearranged product.

The mechanism of enantioselectivity can be explained as follows. The rigid five-membered cyclic intermediate is formed by the reaction of catechol mono allylic ethers with chiral boron reagent (*S*,*S*-**1**), followed by coordination of the allylic oxygen to the boron atom (Figure 1).[9] The re-site of the benzene ring of the substrate may be shielded by one tolyl group of the sulfonamide ligand. Therefore, the approach of the allylic moiety should occur on the si-face giving rise to (*S*)-**4**. The direction of the observed enantioselectivities can be satisfactorily explained by this model.

Figure 1




**3** **4**

A highly enantioselective aromatic Claisen rearrangement of catechol mono allylic ethers could be achieved by employing chiral boron reagent **1** as asymmetric catalyst. This system was proved to be efficient for aromatic Claisen rearrangement avoiding the problematic para rearrangement and abnormal Claisen rearrangement.

### References and Notes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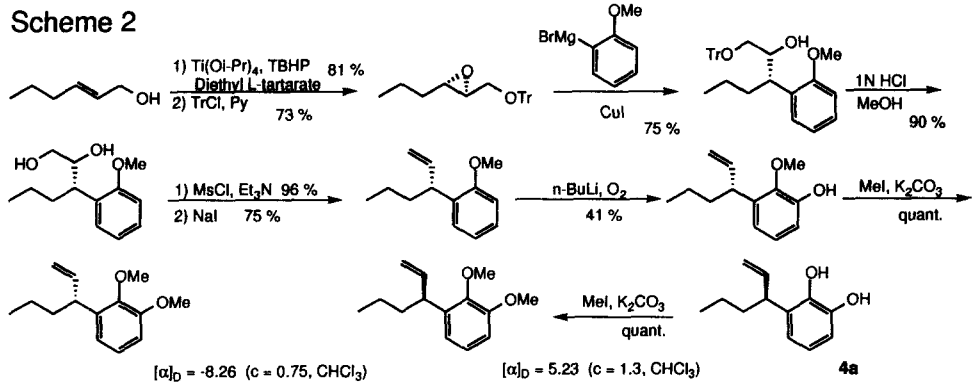
4. Kazmaier, U.; Krebs, A. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2012-2014.
5. See reference 1a.
6. The catechol mono allylic ether derivatives could be easily prepared from mono protected catechol derivatives with commercially available allylic alcohol by Mitsunobu reaction and following deprotection.
7. The absolute chemistry of ortho-substituted catechol derivatives **4a** was determined by comparison of $[\alpha]_D$ value with that of authentic sample. The procedure for preparing authentic sample is shown in Scheme 2.


Scheme 2




8. Other products could not be detected by 300 MHz $^1$H NMR of the reaction mixture.
9. To confirm the coordination of allylic oxygen to the boron atom, we also examined the NMR study of the complex of 2-methoxyphenol and chiral boron reagent **1** in $CDCl_3$ at room temperature. The chemical shift of the methoxy group shifted to higher field by 0.44 ppm (2-methoxyphenol; 3.89 ppm, chiral complex; 3.45 ppm), possibly due to the anisotropic effect of the tolyl group through the coordination of methoxy oxygen to the boron atom.

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