Enantioselective Claisen rearrangement of difluorovinyl allyl ethers

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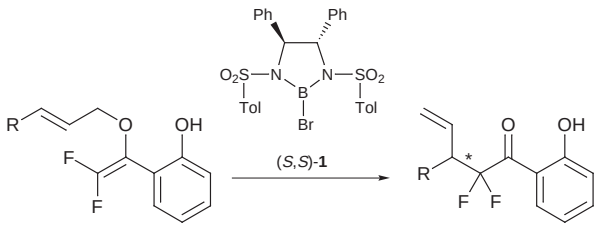
The enantioselective Claisen rearrangement of difluorovinyl allyl ethers was achieved, for the first time, in moderate to good enantioselectivity using a chiral boron reagent as the Lewis acid.

The development of a preparative method for chiral organofluorine compounds is very important in the field of medicinal chemistry.[1] The Claisen rearrangement of difluorovinyl allyl ethers is a powerful tool for the synthesis of β-substituted α,α-difluorocarbonyl compounds.[2] Although enantioselective versions of the Claisen rearrangement have been studied for the construction of chiral molecules,[3] there has been no report dealing with the reaction of difluorovinyl allyl ethers. We recently reported the highly enantioselective aromatic Claisen rearrangement of *o*-allyloxyphenol derivatives mediated by the chiral boron reagent **1**.[4] The efficiency of this system is based on the σ-bond formation of the chiral boron reagent **1**[5] with the phenolic hydroxy group in the substrate and the subsequent coordination of the ethereal oxygen to the boron atom to form a rigid chiral environment in the substrate and to promote the reaction at low temperature. We report herein the application of this system to the enantioselective Claisen rearrangement of difluorovinyl allyl ethers (Scheme 1).

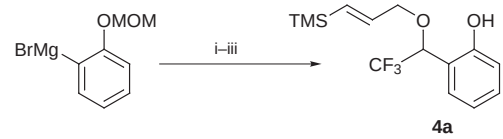


Scheme 1

The substrate **2** having a phenolic hydroxy group was selected, because of the importance of a binding site to the chiral boron reagent **1** in forming a coordinated cyclic intermediate and promoting the reaction. Compound **4a** was prepared from the reaction of 2-methoxymethoxyphenylmagnesium bromide with gaseous trifluoroacetaldehyde generated easily by the reaction of 2 equiv. of trifluoroacetaldehyde ethyl hemiacetal with P_2O_5 at 100 °C, followed by the allylation of the hydroxy group by using 1.2 equiv. of NaH and 1.5 equiv. of (*E*)-1-bromo-3-trimethylsilylprop-2-ene and deprotection under acidic conditions (Scheme 2). Other compounds **4b–d** were also synthesized by the same procedure (32–57% yield). Compound **4** was converted to **2** *via* elimination of fluoride by treatment with 2.5 equiv. of Bu^nLi at −78 to 0 °C in Et_2O. After neutral workup, the vinyl ether **2** was treated with 1.5 equiv. of (*S*,*S*)-**1** in the presence of 1.5 equiv. of Et_3N in CH_2Cl_2 at −78 °C and then the mixture was stirred at ambient temperature to give the rearranged product **3**. The results are summarized in Table 1.

In the chiral boron-mediated Claisen rearrangement, the reaction temperature and enantioselectivity were found to be affected by the configuration of the olefin (*E* or *Z*) and the steric bulkiness of the substituent R at the γ-position. Thus, in the case of **4a** having a TMS substituent, the reaction proceeded at −78 °C to give **3a** with high asymmetric induction (entry 1), while in the reaction of the substrate derived from **4b** having an *E* primary alkyl substituent, a slightly higher temperature was required, giving rise to the product **3b** with moderate selectivity (entry 2).[7] With the *Z* substrate derived from **4c**, the direction of asymmetric induction was opposite to that with *E* substrate **4b** (entry 3).

The absolute stereochemistry of **3d** was determined as shown in Scheme 3. The diastereoselective Claisen rearrangement of **5**



Scheme 2 *Reagents and conditions*: i, trifluoroacetaldehyde generated from its hemiacetal with P_2O_5, THF, 0 °C, 92%; ii, NaH (1.2 equiv.), (*E*)-1-bromo-3-trimethylsilylprop-2-ene, THF–DMF, room temp.; iii, 10% HCl, MeOH, reflux, 31% over 2 steps.

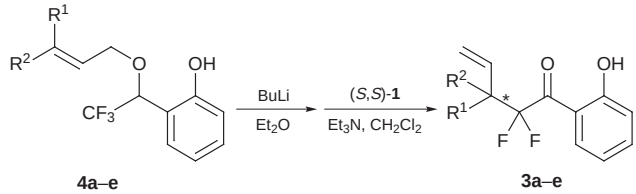
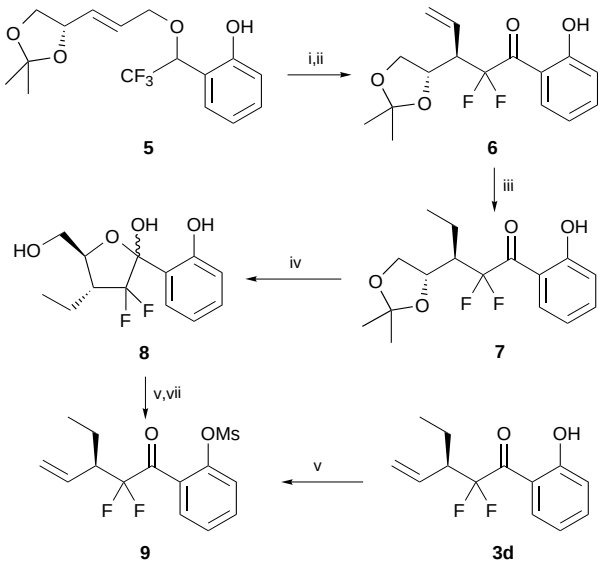


Table 1 The enantioselective Claisen rearrangement of difluorovinyl allyl ethers

Entry	**4**	R^1	R^2	*T*/°C	*t*/h	**3**[a]	Yield (%)[b]	Ee (%)
1	**4a**	H	TMS	−78	3	**3a**	60	85[c]
2	**4b**	H	Pr	−78→−20	5	**3b**	39	41[d]
3	**4c**	Pr	H	−78→−15	5	**3c**	55	55[d]
4	**4d**	Et	H	−78→−15	6	**3d**	58	43[d]
5	**4e**	c-Hex	H	−78→−15	3	**3e**	90	56[d]

[a] Ref. 6. [b] Isolated yield based on **4**. [c] Optical purity determined by HPLC using a Chiralcel OD column. [d] Optical purity was determined by HPLC using a Chiralcel AD column.



Scheme 3 *Reagents and conditions*: i, Bu^{n}Li, Et_2O; ii, toluene, 70 °C, 47% over 2 steps (5:1); iii, H_2, Pd/C, MeOH, 79%; iv, 10% HCl, THF, 60 °C; v, MsCl, Et_3N, CH_2Cl_2, vi, NaI, butanone, reflux; vii, Zn, AcOH, H_2O–THF, 65% from **7**.

smoothly proceeded to give **6** as a major isomer (47%, 5:1), which has an *R* configuration at the newly formed chiral center.[8] Hydrogenation of the olefin of **6** (79%) and the subsequent deprotection of the acetonide group by acid treatment gave compound **8** as an anomeric mixture. After mesylation of the primary and phenolic hydroxy groups of **8**, the product was converted to the olefin **9** in 65% yield (four steps). The enantioselective Claisen rearrangement product **3d** was also converted to **9** by mesylation. Determination of the absolute stereochemistry of **3d** as *R* configuration could be achieved by comparison of the specific rotation of each compound.

The observed enantioselectivity is possibly explained as shown in Fig. 1. The six-membered intermediate is formed by the attachment of the chiral boron reagent **1** to the phenolic hydroxy group, and the subsequent coordination of the ethereal oxygen to the boron atom. In the case of (*S*,*S*)-**1** and the *Z* isomer of **2**, the *Si* face of the difluorovinyl ether moiety is shielded by

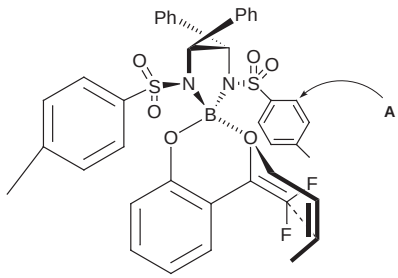
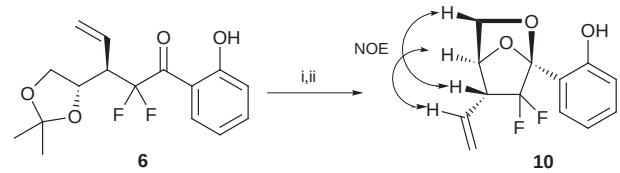


Fig. 1



Scheme 4 *Reagents and conditions*: i, 10% HCl, THF, 60 °C; ii, toluene, 100°C, 63% over 2 steps.

the tolylsulfonyl group (**A**), thus the allylic moiety approaches preferably from the *Re* face to avoid steric interaction with **A** in the chair like transition state.

In conclusion, we have demonstrated for the first time enantioselective Claisen rearrangement of difluorovinyl allyl ethers using the chiral boron reagent **1** and the substrate **2** having a phenolic hydroxy group to form an efficient chiral environment.[9]

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Notes and references

1 *Biomedicinal Aspects of Fluorine Chemistry*, ed. R. Filler and Y. Kobayashi, Elsevier Biomedical Press and Kodansha Ltd, 1982; J. T. Welch, *Tetrahedron*, 1987, **43**, 3123; *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, ed. R. Filler, Y. Kobayashi and L. M. Yagupolskii, Elsevier, Amsterdam, 1993.

2 W. B. Metcalf, E. T. Jarvi and J. P. Burkhart, *Tetrahedron Lett*., 1985, **26**, 2861; G.-Q. Shi, Z.-Y. Cao and W.-L. Cai, *Tetrahedron*, 1995, **51**, 5011; G.-Q. Shi and W.-L. Cai, *J. Org. Chem*., 1995, **60**, 6289; H. Greuter, R. W. Lang and A. J. Roman, *Tetrahedron Lett*., 1988, **29**, 3291.

3 K. Maruoka, H. Banno and H. Yamamoto, *J. Am. Chem. Soc*., 1990, **112**, 7791; K. Maruoka, H. Banno and H. Yamamoto, *Tetrahedron*: *Asymmetry*, 1991, **2**, 647; K. Maruoka and H. Yamamoto, *Synlett* 1991, 793; K. Maruoka, S. Saito and H. Yamamoto, *J. Am. Chem. Soc*., 1995, **117**, 1165; E. J. Corey and D.-H. Lee, *J. Am. Chem. Soc*., 1991, **113**, 4026; E. J. Corey and R. S. Kania, *J. Am. Chem. Soc*., 1996, **118**, 1229; U. Kazmaier and A. Krebs, *Angew. Chem., Int. Ed. Engl*., 1995, **34**, 2012; A. Krebs and U. Kazmaier, *Tetrahedron Lett*., 1996, **37**, 7945.

4 H. Ito, A. Sato and T. Taguchi, *Tetrahedron Lett*., 1997, **38**, 4815.

5 E. J. Corey, R. Imwinkelried, S. Pikul and Y.-B. Xiang, *J. Am. Chem. Soc*., 1989, **111**, 5493.

6 Optical rotation ([α]D) was measured in $CHCl_3$ at 26 °C. **3a**: 41.1; **3b**: 18.6; **3c**: −18.3; **3d**: −8.8; **3e**: −20.3.

7 In the absence of Lewis acid, the *E* isomer **2b** smoothly rearranged to **3b** even at room temperature, possibly due to the presence of the phenolic hydroxy group, to form an intramolecular hydrogen bond between the ethereal oxygen.

8 The relative stereochemistry of compound **6** was determined *via* conversions to **10** and a NOESY experiment, as shown in Scheme 4.

9 Regarding the removal of the hydroxyphenyl moiety, we examined some conditions, *i.e*. oxidative degradation of the aromatic ring and cleavage of the carbon–carbon bond of the aryl ketone moiety (Baeyer–Villiger and Schmidt rearrangement). In these experiments, although the aromatic ring was absent from the ^1H NMR analysis of the crude mixture, we were unable to find a clean method for cleavage of the hydroxyphenyl moiety.

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