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Tetrahedron Letters 45 (2004) 6337–6341
Tetrahedron Letters

Boron trifluoride-induced reactions of phenylglycidyl ethers: a convenient synthesis of enantiopure, stereodefined fluorohydrins

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Received 30 April 2004; revised 16 June 2004; accepted 16 June 2004
Available online 10 July 2004

Abstract—Ring-opening hydrofluorination of enantiomerically pure (2*S*,3*S*)-3-arylglycidyl ethers (aryl = phenyl, 4-trifluoromethylphenyl) by boron trifluoride–diethyl ether under mild conditions provides β-fluoro alcohols in good yield in a stereospecific manner with complete regiocontrol.

Over the last years, the demand for optically active fluorinated compounds has dramatically increased because of their applications in many different areas. In biomedicine, and in the important field of enzyme inhibitors, for example, fluoro peptide isosteres possessing an increased stability toward enzymatic degradation and improved bioavailability in combination with high activity and selectivity have arosen from structure–activity relationship studies.[1] In addition, several fluorine-containing molecules are the basis for commercial drugs used as anti-viral, anti-cancer, and anti-bacterial agents.[2]

A different field where optically active fluorine compounds have gained progressive importance is in the determination of enantiomeric composition of chiral, nonracemic compounds by ^{19}F NMR spectroscopy analysis. Thus, besides the classical α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA, Mosher's reagent), α-methoxy-α-methyl-(pentafluorophenyl) acetic acid (MMPA), and α-cyano-α-fluorophenylacetic acid (CFPA),[3a] new chiral derivatizing agents (CDA's), such as α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA)[3b] and (*R*)-2-fluorophenylacetic acid (AFPA),[3c,d] featuring a fluorine atom directly bound to the stereogenic carbon have been recently incorporated to the chemist's toolkit.

In response to this increasing demand, several methods have been developed for the preparation of optically active fluoro alcohols, mostly relying on the ring opening of epoxides with nucleophilic fluorine from different sources. These procedures uniformly suffer from low yields and, when desymmetrization of *meso* epoxides is involved, from poor enantioselectivity. In this respect, the asymmetric ring opening of *meso* or racemic epoxides by molar amounts of a salen metal complex in the presence of a fluoride source affording fluorohydrins with moderate enantioselectivities has been recently achieved.[4]

On the other hand, optically active fluorohydrins have also been obtained by the ring opening of enantiomerically pure epoxyalcohols with Et_4NF-*n*HF in the presence of a titanium catalyst,[5b] with variable degrees of stereospecificity, regioselectivity, and yield.[5a] Finally, fluoro alcohols have been deracemized by enzymatic hydrolysis of the corresponding acetates or chloroacetates or by esterification of racemic fluorohydrins.[6] In any case, all the reported methods for the preparation of stereodefined fluoro alcohols in enantiopure form present severe limitations so that additional synthetic efforts in this field are fully warranted.

In connection with our research on the synthesis of new modular ligands for asymmetric catalysis from synthetic

Keywords: Fluoroalcohols; Fluorohydrins; Boron trifluoride–etherate; Ring-opening; Epoxides; Epoxyethers.
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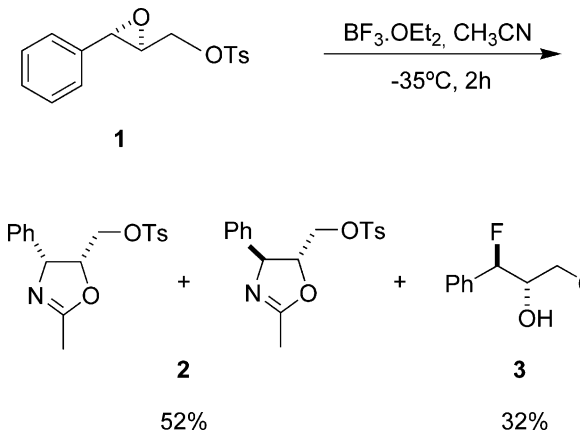
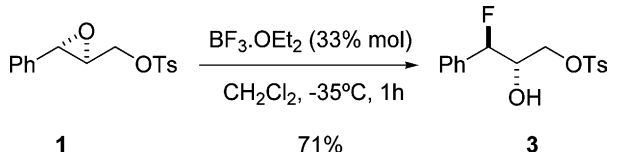
doi:10.1016/j.tetlet.2004.06.069



Scheme 1.



Scheme 2.

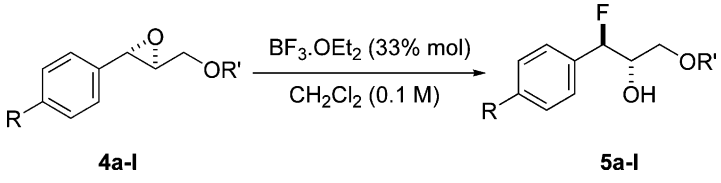
epoxides,[7] we investigated the synthesis of oxazolines **2** from (2*S*,3*S*)-3-phenylglycidyl *p*-toluenesulfonate **1**[8a] and acetonitrile by using equimolar amounts of boron trifluoride–diethyl ether to catalyze the process.[8b] We were surprised to find that, under these reaction conditions, boron trifluoride was able to induce the ring-opening of the oxirane to afford as a by-product fluorohydrin **3** in a completely regio and stereoselective manner (Scheme 1).

Given the intrinsic interest of enantiopure fluoro alcohols, the observation of this behaviour prompted us to investigate the use of $BF_3{\cdot}OEt_2$ as a suitable reagent for the ring-opening hydrofluorination of enantiopure epoxides. In fact, boron trifluoride–diethyl ether complex has already been used as fluorinating agent and, in some cases, as a catalyst in fluorination reactions (for instance, in the preparation of alkyl fluorides by decomposition of alkyl fluoroformates, in the fluorination of carboxyl groups, or in the preparation of fluorinated ethers from alcohols),[9] but its use as a fluoride source in the ring-opening of epoxides remains practically unexplored.[10]

To achieve our goal, we first decided replacing CH_3CN by CH_2Cl_2 in order to suppress the reaction pathway leading to the oxazoline products. After some experimentation we were able to develop optimized reaction conditions for the preparation of **3** (Scheme 2).

The optimized reaction conditions were next applied to the ring opening of a family of enantiopure (>99% ee) (2*S*,3*S*)-3-phenylglycidol derivatives[11] **4a–i** (Scheme 3) providing the results shown in Table 1.

Noteworthy, enantiopure β-fluoro alcohols can be obtained in good yield and with complete regiocontrol by this operationally simple protocol,[12] which takes place under very mild conditions. This represents a clear difference with the previously reported procedures for the hydrofluorinating ring-opening of epoxides, where mixtures of regioisomers are obtained in all cases.[13] On the other hand, the high reactivity exhibited by phenylglycidyl ethers toward $BF_3{\cdot}OEt_2$ at low temperature is remarkable. Thus, the fast reactions observed in this study contrast with the long reaction times required to induce analogous epoxide ring-opening with other



Scheme 3.

Table 1. Ring-opening hydrofluorination of enantiomerically pure phenylglycidol ethers

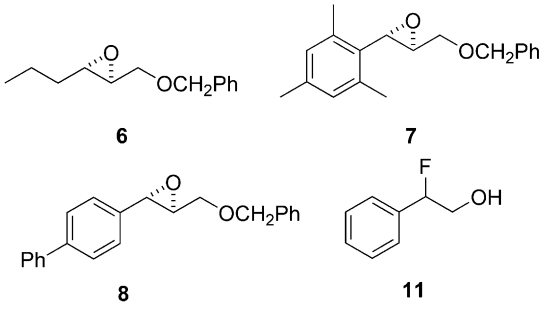
Entry	R	R′	*T* °C	*t*	Yield (%)
a	H	CH_3	−35	1 h	46
b	H	CH_2Ph	−35	1 h	75
c	H	$CHPh_2$	−35	1 h	65
d	H	CPh_3	−35	1 h	58
e	H	TBDPS	−35	1 h	36
f	H	$CH(CH_3)Ph$	−78	15 min	48
g	H	*o*-MeOBn	−78	15 min	38
h	H	*m*-MeOBn	−78	15 min	53
i	H	*p*-MeOBn	−78	15 min	0[a]
j	CF_3	*o*-NO_2Bn	−35	1 h	34
k	CF_3	CH_2Ph	−35	3 h	36
l	CF_3	TBDPS	0	3 h	44

[a] See text.

fluoride sources.[14] Finally, another interesting characteristic of this process is its stereospecificity. Thus, when the sequences started from enantiopure *trans*-phenylglycidol, the ^{19}F NMR spectrum of the resulting fluoro alcohols **5a–i** exhibited in all cases a single signal, indicating that diastereomerically pure *anti*-fluoro alcohols had been obtained. Since the stereogenic center at C-2 is not affected by the ring-opening, the optical purity of the substrates is conserved during the reaction.

With respect to yield, the observed variability reflects both the ease of ether deprotection by the employed Lewis acid[15] and the ease for Lewis acid-induced rearrangement to β-oxy aldehydes of the substrates.[16] The results observed with the *o*-, *m*-, and *p*-methoxybenzyl ethers of phenyl glycidol deserve a separate comment. With all three substrates, a very fast reaction takes place, complete conversion being recorded after only 15 min at −78 °C. However, whereas with the *o*- and *m*-substituted substrates the expected fluoro alcohol was obtained, the *p*-substituted one underwent a completely different reaction and a 1,3-dioxolane product, arising from intramolecular Friedel–Crafts attack was obtained.[17]

In view of the results observed with phenylglycidyl ethers, we wanted to test the scope of the $BF_3{\cdot}Et_2O$ induced hydrofluorinating ring-opening reaction and, to this end, we prepared the glycidyl benzyl ethers **6–8**.



When the aliphatic epoxy ether **6**[18] was submitted to the same reaction conditions of Scheme 3, no fluorohydrin at all could be detected, and the starting material was recovered from the reaction mixture even after extended treatment at 0 °C. In the case of oxiranes **7**[19] and **8**,[20] whose structures involve electronically rich aryl substituents, rather unstable β-benzyloxy aldehydes[16] were obtained as the reaction products.

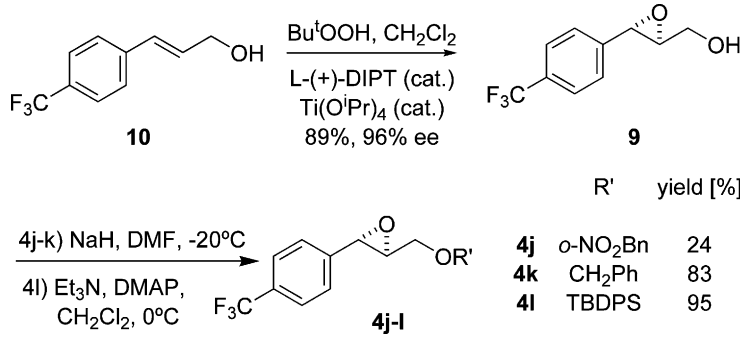
As discussed above, one of the areas where enantiopure compounds containing fluorine atoms directly bound to stereogenic centers are finding more intense application is as derivatizing agents for the determination of enantiomeric composition by ^{19}F NMR spectroscopy. Since the results obtained in the ring-opening of **4a–i** and **7–8** suggested that the presence of electron-withdrawing groups on the aryl substituent of the glycidyl derivative could favour the reaction pathway leading to fluoro alcohols over those involving epoxide rearrangement,[16] we decided to study the ring-opening hydrofluorination of glycidyl ethers **4j–l**, which incorporate a trifluoromethyl substituent on the aromatic ring. In this way, enantiopure alcohols containing a dual fluorine probe could be obtained.

The required starting material, enantiopure (2*S*,3*S*)-3-4-(trifluoromethyl)phenylglycidol **9**[21] could be readily prepared in this instance by catalytic Sharpless epoxidation of (*E*)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol **10** in 89% yield and 96% ee. Final conversion into ethers **4j–l** was performed as shown in Scheme 4.

As shown in Table 1, the ring opening of all three glycidyl ethers took place leading to the desired fluorohydrins **5j–l**. Interestingly, the highest yield is recorded for the silyl derivative **5l**, which can be very easily deprotected and, hence, offers interesting possibilities for application as an enantiopure derivatizing agent precursor.[3c]

With respect to reaction mechanism, the high tendency to ring-opening exhibited by epoxyethers **4a–l** can probably be ascribed to assistance by the alkoxy substituent to complexation of BF_3, as it is assumed to happen in the Ti(IV)-mediated ring-opening of epoxyalcohols.[22] In favour of this hypothesis, when styrene oxide was submitted to the standard ring-opening conditions (−35 °C, 1 h) a mixture of aldol type products arising from initial epoxide rearrangement was predominantly formed, and 2-fluoro-2-phenylethanol (**11**) could be isolated in less than 8% yield.

In summary, the course of the low temperature reaction of **4a–j**, epoxyethers with $BF_3{\cdot}OEt_2$ is a convenient



Scheme 4.

procedure for the synthesis of enantiopure, stereodefined fluorohydrins, but its course is strongly dependent on the nature of the substrate. In any case, the fluoro alcohols obtained by this procedure are extremely pure from both the regiochemical and the stereochemical point of view. Among them, **5j–l**, containing a dual fluorine marker are currently being elaborated into new reagents for the fast and reliable ^{19}F NMR based determination of enantiomeric excesses.

Acknowledgements

Finantial support from DGI-MCYT (BQU2002-02459), DURSI (2001SGR50) and Fundación Ramón Areces is gratefully acknowledged. G.I.-G. thanks MECYD for a post-doctoral fellowship (Ayudas para Estancias de Doctoresy Tecnólogos Extranjeros en España).

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