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β-Fluoroamphetamines via the Stereoselective Synthesis of Benzylic Fluorides

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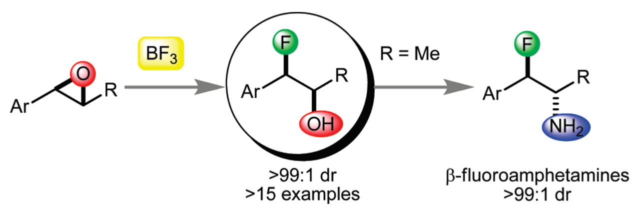
ABSTRACT



A range of substituted aryl epoxides undergo efficient ring-opening hydrofluorination upon treatment with 0.33 equiv of $BF_3 \cdot OEt_2$ in CH_2Cl_2 at −20 °C to give the corresponding *syn*-fluorohydrins, consistent with a mechanism involving a stereoselective S_N1-type epoxide ring-opening process. The benzylic fluoride products of these reactions are valuable templates for further elaboration, as demonstrated by the preparation of a range of aryl-substituted *β*-fluoroamphetamines.

The incorporation of fluorine into organic molecules frequently has a dramatic impact on their physical, chemical, and biological properties,[1] and compounds bearing fluorine at stereogenic centers are of mounting interest in medicinal chemistry.[2] The benzylic fluoride motif is an effective isosteric replacement for benzylic C−H or C−OH groups in many pharmaceutical and agrochemical candidates,[3] and chiral benzylic fluorides have found application in the synthesis of fluorinated ferroelectric liquid crystals.[4] However, a shortage of reliable, generally applicable methods for the stereoselective synthesis of this class of compounds has meant that this motif remains underutilized in drug discovery.[5] Nucleophilic fluorination strategies toward benzylic fluorides typically suffer from partial or total racemization/epimerization due to the intermediacy of benzylic carbocations.[5] A few isolated examples of the stereoselective ring-opening hydrofluorination of aryl epoxides using $BF_3 \cdot OEt_2$ have been reported,[6] although the generality of this process has yet to be explored. Considering the significant practical and economic benefits (i.e., low cost, high fluorine content and ease of handling in standard glassware) we investigated the utility of $BF_3 \cdot OEt_2$ as a nucleophilic fluorine source and report herein our results within this area.

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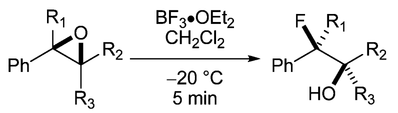
Scheme 1



1-8 **9-14**

epoxide	R_1	R_2	R_3	fluorohydrin	yield %
(±)-**1**	H	H	H	(±)-**9**	8[a]
(±)-**2**	Me	H	H	(±)-**10**	0
(±)-**3**	H	Me	H	(±)-**11**	83[b]
(*R*,*R*)-**3**[c]	H	Me	H	(*R*,*R*)-**11**	81[b,d]
(±)-**4**	H	H	Me	(±)-**11**	5[a]
(±)-**5**	Me	H	Me	(±)-**12**	13[a]
(±)-**6**	Me	Me	H	(±)-**12**	0
(±)-**7**	H	Me	Me	(±)-**13**	0
(±)-**8**	Me	Me	Me	(±)-**14**	8[b]

[a] Calculated from ^{19}F NMR spectroscopic analysis with fluorobenzene standard. [b] Isolated yield of a single diastereoisomer (>99:1 dr). [c] ~90% ee. [d] 92% ee.

Under optimized conditions, treatment of racemic (*E*)-*β*-methylstyrene oxide **3** with 0.33 equiv of BF_3·OEt_2 in CH_2Cl_2 at −20 °C for 5 min gave fluorohydrin **11** as the major product in >99:1 dr, which was isolated in 83% yield and >99:1 dr, consistent with the transfer of all three fluorine atoms of BF_3·OEt_2 (Scheme 1).[7] The relative *syn*-configuration within **11** was unambiguously established by single-crystal X-ray analysis of the *p*-nitrobenzoate derivative **15** (Figure 1). In the enantiopure series, ring-opening hydrofluorination of (*R*,*R*)-**3** (~90% ee)[8] gave fluorohydrin (*R*,*R*)-**11** in 81% yield, >99:1 dr and 92% ee[9] (Scheme 1). Treatment of (*Z*)-*β*-methylstyrene oxide **4** with BF_3·OEt_2 under the same conditions gave a mixture of products containing 5%[10] of *syn*-fluorohydrin **11** and phenylpropan-2-one as the major component. Similar reaction with epoxides **1**, **2**, and **5−8** also gave rise to complex mixtures of products with only very low levels of fluorine incorporation (≤13%)[10] being observed (Scheme 1).

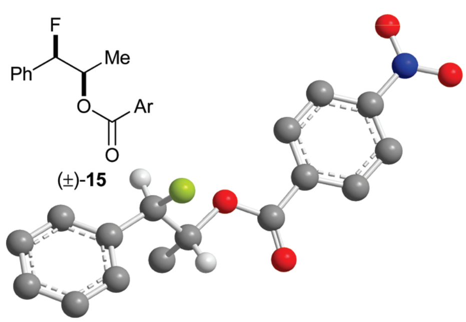


Figure 1. Chem3D representation of the single-crystal X-ray structure of (±)-**15** (some H atoms omitted for clarity). Ar = *p*-$C_6H_4NO_2$.

The formation of *syn*-fluorohydrin **11** from *trans*-epoxide **3** is consistent with a mechanism involving co-ordination of BF_3 to the oxirane oxygen and subsequent rupture of the C−O bond to generate benzylic carbocation **16** in conformation **16A**; transfer of fluorine and workup gives *syn*-fluorohydrin **11**. In the case of *cis*-epoxide **4**, the carbocation is generated in conformation **16B**, which suffers from destabilizing nonbonded interactions between the phenyl and methyl groups. A C−C bond rotation to relieve this strain may place the C(*β*)-H bond coplanar to the empty p-orbital (e.g., in conformation **16C**); a subsequent [1,2]-H-atom shift results in the formation of phenylpropan-2-one, the observed major product (Figure 2). This simplistic mechanistic rationale is also able to successfully account for the low levels of fluorine incorporation observed for the range of epoxides **1**, **2**, and **5−8**, as in none of these cases is there a significant steric bias for the benzylic carbocation to be sufficiently long-lived in its initial conformation for efficient fluorine transfer to occur before side reactions can intervene.

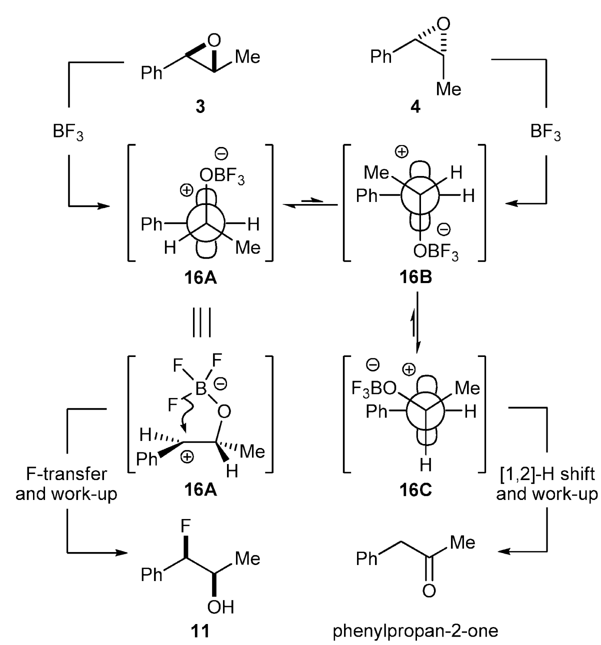


Figure 2. Postulated mechanism for ring-opening hydrofluorination with BF_3·OEt_2.

The functional group tolerance of this reaction was next probed. Treatment of epoxides **17−19** and **21−24** with BF_3·OEt_2 gave the corresponding *syn*-fluorohydrins **27−29** and **31−34** as the major products in >99:1 dr, which were isolated in good yields. Competing isomerization processes

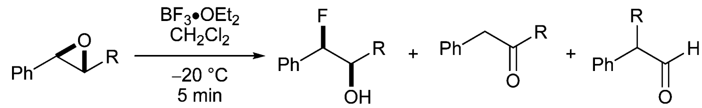
(7) BF_3·OEt_2 has previously been demonstrated to transfer all three fluorine atoms during the ring-opening hydrofluorination of aryl epoxides, necessitating the use of only 0.33 equiv of this reagent; see ref 6c.

(8) A sample of (*R*,*R*)-**3** was prepared by Shi epoxidation of *trans*-*β*-methylstyrene; see: Wang, Z. X.; Shu, L.; Frohn, M.; Tu, Y.; Shi, Y. *Org. Synth.* **2003**, *80*, 9. This procedure has been reported to give (*R*,*R*)-**3** in 89−92% ee.

(9) The enantiomeric excess of (*R*,*R*)-**11** was determined by conversion to the corresponding Mosher's ester; see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

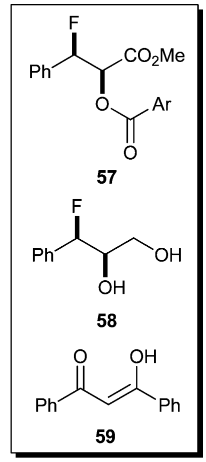
(10) The percentage of fluorine incorporation into the reaction products was determined by ^{19}F NMR spectroscopic analysis with a fluorobenzene standard.

Scheme 2[a]



17-26 → **product A** syn-fluorohydrin **27-36** + **product B** ketone **37-46** + **product C** aldehyde **47-56**

epoxide	R	ratio A:B:C	product A yield %	product B yield %	product C yield %
17	CH_2Cl	78:22:0	**27**, 70	**37**, 0	**47**, 0
18	CH_2Br	78:22:0	**28**, 72	**38**, 21	**48**, 0
19	CH_2N_3	92:8:0	**29**, 65	**39**, 0	**49**, 0
20	$CH_2OTBDMS$	35:10:55	**30**, 31	**40**, 0	**50**, 41
21	CH_2OTs	84:16:0	**31**, 84	**41**, 16	**51**, 0
22	CH_2CH_2OTs	94:6:0	**32**, 85	**42**, 0	**52**, 0
23	COPh	69:31:0[b]	**33**, 42	**43**, 0	**53**, 0
24	CO_2Me	100:0:0[c]	**34**, 65	**44**, 0	**54**, 0
25	SO_2Ph	0:0:100	**35**, 0	**45**, 0	**55**, 91
26	Ph	0:0:100	**36**, 0	**46**, 0	**56**, 80



[a] All Compounds Are Single Diastereoisomers (>99:1 dr). [b] A 69:31 mixture of **33** and **59** was produced. [c] Reaction required 30 min to proceed to conversion. Ar = p-$C_6H_4NO_2$.

to give carbonyl compounds were observed in most cases; in fact, migration of the R substituent to give aldehydes **50**, **55**, and **56** represented the major (and in the latter two cases exclusive) product upon reaction of epoxides **20**, **25**, and **26**, which bear R groups of high migratory aptitude (Scheme 2). The relative *syn*-configurations within fluorohydrins **27**−**34** were assigned by analogy to that unambiguously established for **11**. In support of these assignments, the relative *syn*-configuration within **34** was unambiguously determined by single-crystal X-ray analysis of the *p*-nitrobenzoate derivative **57** (Figure 3), and the relative *syn*-configurations within **30**, **31** and **34** were correlated via the common diol **58**. The ring-opening hydrofluorination of some *O*-protected 3-phenyl glycidols (including **21**) with $BF_3{\cdot}OEt_2$ has previously been reported by Pericàs et al., with *anti*-configurations being assigned to the fluorohydrin products on the basis of the reaction proceeding via an S_N2-type epoxide opening.[6c] In light of our results, however, the stereochemistry of these fluorohydrin products has been reassigned by Pericàs et al. as *syn*.[11]

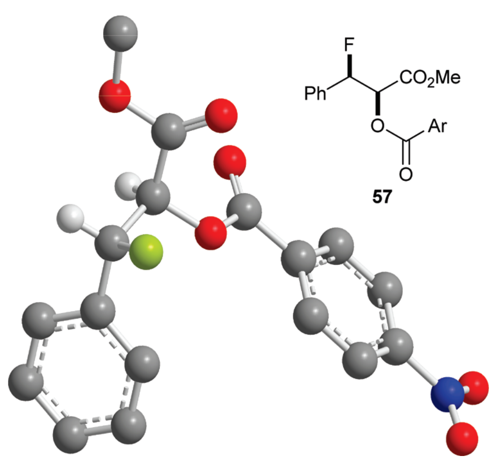


Figure 3. Chem3D representation of the single-crystal X-ray structure of **57** (some H atoms omitted for clarity). Ar = p-$C_6H_4NO_2$.

The effect of the electronic nature of the aryl group was investigated by application of the optimized reaction conditions to a range of (*E*)-*β*-methylstyrene oxides **60**−**70** (≥90:10 dr) bearing aryl substituents with Hammett σ^+ substituent constants ranging from −0.78 to +0.61.[12] Ring-opening hydrofluorination of **63** and **64** (X = *p*-F, *m*-OMe) gave the corresponding fluorohydrin products **74** and **75** (>99:1 dr). The more electron-deficient species **65**−**69** (X = *p*-Cl, *p*-Br, *m*-F, *m*-Cl, *m*-Br) required a reaction time of 10 min for complete consumption of starting materials to give fluorohydrins **76-80** (>99:1 dr). Fluorohydrins **74**−**80** were isolated in good yields after chromatography. However, reaction of the electron-rich species **60**−**62** (X = *p*-OMe, *p*-Me, *p*-Ph) resulted in mixtures of products, including the corresponding arylpropan-2-one as a major component. Reaction of **70** (X = *p*-CF_3) proceeded with incomplete conversion to give a mixture of products including fluorohydrin **81**, although this was not isolated in pure form. The relative configurations within fluorohydrins **74-80** were assigned as *syn* by analogy to that unambiguously proven for **11**; in all cases, the C(1)*H*−C(2)*H* coupling constant was 6.8 Hz, which is supportive of the assigned *syn*-stereochemistry.[13] Assuming that these reactions proceed via the intermediacy of a benzylic carbocation, these results suggest that a compromise in carbocation stability versus reactivity

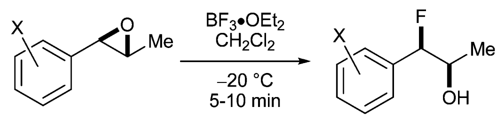
(11) See the correction to: Rodríguez-Escrich, S.; Popa, D.; Jimeno, C.; Vidal-Ferran, A.; Pericàs, M. A. *Org. Lett.* **2005**, *7*, 3829; *Org. Lett.* **2010**, *12*, DOI: 10.1021/ol1008735.

(12) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.

(13) This is consistent with the value of 7.1 Hz observed for *syn*-fluorohydrin **11** versus 4.8 Hz for the corresponding *anti*-diastereoisomer. A correlation between relative stereochemistry and vicinal ^{1}H NMR ^3J coupling constant for a range of *β*-fluoro-*β*-phenylamines has previously been reported; see: Hamman, S.; Benaïssa, T.; Béguin, C. G. *Magn. Reson. Chem.* **1988**, *26*, 621.

may be necessary for successful incorporation of fluorine, meaning that the rate of both cation formation and cation trapping by fluorine must outpace competing side reactions (Scheme 3).

Scheme 3



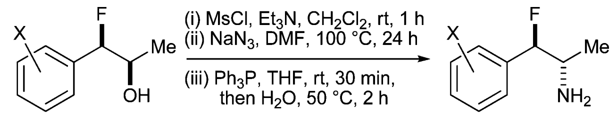
60-70 **71-81**

epoxide	dr	X	σ⁺ (X)	time	fluorohydrin	yield %[a]
60	>99:1	*p*-OMe	−0.78	5 min	**71**	0
61	90:10	*p*-Me	−0.31	5 min	**72**	0
62	98:2	*p*-Ph	−0.18	5 min	**73**	0
63	94:6	*p*-F	−0.07	5 min	**74**	76
64	93:7	*m*-OMe	+0.05	5 min	**75**	81
65	94:6	*p*-Cl	+0.11	10 min	**76**	76
66	94:6	*p*-Br	+0.15	10 min	**77**	78
67	95:5	*m*-F	+0.35	10 min	**78**	67
68	92:8	*m*-Cl	+0.40	10 min	**79**	64
69	91:9	*m*-Br	+0.41	10 min	**80**	67
70	94:6	*p*-CF_3	+0.61	10 min	**81**	0

[a] Isolated yield of a single diastereoisomer (>99:1 dr).

The utility of these fluorinated building blocks was demonstrated by the synthesis of a range of aryl-substituted *β*-fluoroamphetamines,[14] a motif that has been utilized in SAR studies toward agrochemical fungicides[15] and nitric oxide synthase inhibitors.[16] ^{18}F-Labeled *β*-fluoroamphetamines have also been studied as potential radiotracers for in vivo diagnostic imaging.[17] Sequential treatment of *syn*-fluorohydrins (±)-**11**, (*R*,*R*)-**11**, and **75**−**80** with mesyl chloride and sodium azide gave the corresponding *anti*-*β*-fluoroazides (±)-**82**, (1*R*,2*S*)-**82**,[18] and **83**−**88**, with subsequent Staudinger reduction providing *anti*-*β*-fluoroamphetamines (±)-**89**, (α*S*,*β**R*)-**89**,[18] and **90**−**95** in good yield and as single diastereoisomers (Scheme 4).

Scheme 4



11, **75-80** **89-95**

fluorohydrin	X	β-fluoroazide yield %[a]	β-fluoroamphetamine yield %[a]
(±)-**11**	H	(±)-**82**, 77	(±)-**89**, 83
(*R*,*R*)-**11**[b]	H	(1*R*,2*S*)-**82**,[c] 84	(α*S*,β*R*)-**89**,[b] 81
(±)-**75**	*m*-OMe	(±)-**83**, 75	(±)-**90**, 90
(±)-**76**	*p*-Cl	(±)-**84**, 75	(±)-**91**, 80
(±)-**77**	*p*-Br	(±)-**85**, 74	(±)-**92**, 78
(±)-**78**	*m*-F	(±)-**86**, 65	(±)-**93**, 80
(±)-**79**	*m*-Cl	(±)-**87**, 63	(±)-**94**, 87
(±)-**80**	*m*-Br	(±)-**88**, 63	(±)-**95**, 96

[a] Isolated yield of a single diastereoisomer (>99:1 dr). [b] 92% ee. [c] 93% ee.

In conclusion, the ring-opening hydrofluorination of a range of substituted aryl epoxides upon treatment with 0.33 equiv of BF_3•OEt_2 in CH_2Cl_2 proceeds rapidly at −20 °C to give the corresponding *syn*-fluorohydrins, consistent with a mechanism involving a stereoselective S_N1-type process. The reaction manifold is able to tolerate a range of functionality within the basic aryl epoxide framework, including modestly electron-withdrawing groups on the aromatic ring. The *syn*-fluorohydrin products of these reactions are useful building blocks for further elaboration, as demonstrated by the preparation of a range of *β*-fluoroamphetamines.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The enantiomeric excesses of (1*R*,2*S*)-**82** and (α*S*,*β**R*)-**89** were determined by chiral GC analyses, for which the authors would like to thank Carole J. R. Bataille.