Tetrahedron Letters 56 (2015) 3373–3377

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Pinacolatoboron fluoride (pinBF) is an efficient fluoride transfer agent for diastereoselective synthesis of benzylic fluorides

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ARTICLE INFO

Article history:
Received 3 December 2014
Accepted 9 December 2014
Available online 16 December 2014

Keywords:
Benzylic fluoride
Epoxide
Nucleophilic fluorination

ABSTRACT

The incorporation of alkoxy ligands within a range of alkoxyfluoroboranes and dialkoxyfluoroboranes results in fluoroborane reagents with attenuated Lewis acidity and increased ability to donate fluoride ion(s) when compared to boron trifluoride itself. Pinacolatoboron fluoride (pinBF), prepared in situ from $BF_3{\cdot}OEt_2$ and bis(*O*-trimethylsilyl)pinacol, has been identified as an efficient fluoride donor which allows highly stereoselective S_N1-type epoxide ring-opening (with retention of configuration) of a range of *trans*-β-methyl-substituted aryl epoxides to give the corresponding *syn*-fluorohydrins. The substrate scope of this transformation is more broad than the analogous protocol using boron trifluoride alone.

Stereodefined organofluorine compounds are of escalating importance across several branches of chemistry,[1] owing to the ability of the C–F bond to modify the physicochemical and biological properties of organic molecules.[2] Chiral benzylic fluorides, for instance, have found application as treatments for neurological disorders[3,4] and atherosclerosis,[5] as nerve gas immunization agents,[6] and in ferroelectric liquid crystal technology.[7] Despite methodological advances in stereoselective fluorination,[8] including the advent of asymmetric protocols,[9] the synthesis of stereodefined benzylic fluorides by nucleophilic fluorination is frequently hampered by competing racemization (or epimerization) due to the intermediacy of benzylic carbocations.[10,11] As part of a research programme into the utility of boron fluorides[12] and fluoroborates[13–15] as inexpensive, atom-economic and easily-handled nucleophilic fluorinating agents,[16] we have reported the ring-opening fluorination of *trans*-β-substituted aryl epoxides upon treatment with $BF_3{\cdot}OEt_2$.[12] This reaction proceeds via stereoselective S_N1-type ring opening with retention of configuration to provide benzylic fluoride building blocks, which we utilized for the synthesis of a range of β-fluoroamphetamines.[12] For example, treatment of epoxide **1** (Ar = Ph) with 0.33 equiv of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −20 °C for 5 min gave *syn*-fluorohydrin **7** in 81% yield. This diastereoselectivity is consistent with initial activation of **1** by co-ordination of BF_3, followed by epoxide cleavage to give benzylic carbocation **5**, followed by intramolecular fluoride transfer to give **7**. This reaction manifold did not accommodate epoxides bearing electron-rich aryl groups: for example, under analogous conditions, the reaction of epoxide **2** (Ar = *p*-Tol) gave ketone **12** as the major product (which was isolated in 38% yield), with no evidence of the corresponding fluorohydrin **8** being noted in either the ^1H or ^{19}F NMR spectra of the crude product mixture. The presence of the electron-donating aryl group presumably serves to increase the stability of the carbocation within **6** (as compared to **5**), which results in a concomitant reduction of the rate of intramolecular fluoride transfer (k_1) from the anionic fluoroborate moiety. Alternative processes such as C–C bond rotation (k_2) to give **10**, and subsequent [1,2]-hydrogen atom shift to give ketone **12**, are thus able to compete (Scheme 1). [12]

A conceptually attractive solution to this limitation is reduction of the Lewis acidity of BF_3: in this scenario the derived 8-B-4[17] fluoroborate form becomes a more powerful fluoride donor, which should be manifest in an increase in the relative rate of fluoride transfer (k_1). In fact, decreasing the Lewis acidity of BCl_3 or BBr_3 by the introduction of hydrido or alkyl B-ligands, or strong π-donor alkoxy or dialkylamido B-ligands,[18,19] is an established strategy to facilitate the ring-opening chlorination or bromination of epoxides[20] and other cyclic ethers[21] by haloborane reagents. The attenuated Lewis acidity of these modified haloborane reagents leads to enhanced chemoselectivity, and helps to minimise or prevent side reactions (e.g., carbocation formation, polymerisation) otherwise induced by the harshly Lewis acidic BCl_3 or BBr_3 reagents. In the first reported example of this tactic, Bell and Ciaccio reported that $(Me_2N)_2BBr$ [prepared in situ by pre-mixing BBr_3 and $B(NMe_2)_3$ in a

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http://dx.doi.org/10.1016/j.tetlet.2014.12.044
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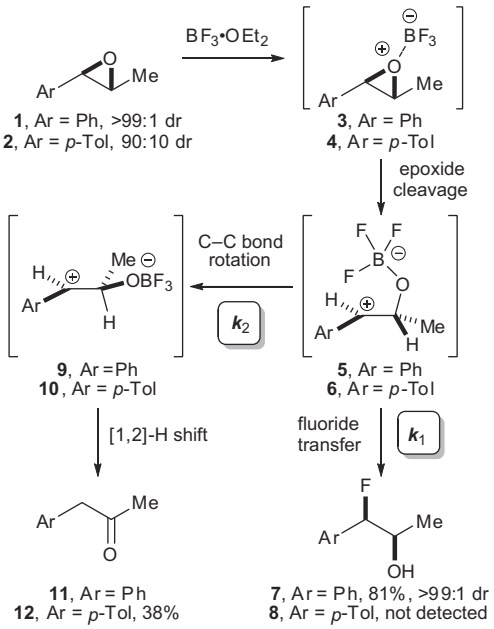
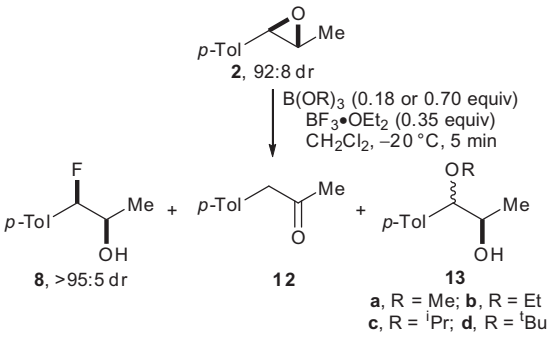


Scheme 1. *p*-Tol = *para*-tolyl.

1:2 ratio] is a convenient reagent for the S_N2-type ring-opening bromination of epoxides.[22] Similarly, Guindon and co-workers have shown that Me_2BBr is a generally effective and highly chemoselective reagent for the S_N2-type ring-opening bromination of epoxides and other cyclic ethers.[23] In addition, Brown and co-workers have described the utility of $(MeO)_2BCl$[24] and $(MeO)_2BBr$[25] [prepared in situ by pre-mixing BCl_3 or BBr_3 respectively with $B(OMe)_3$] as reagents for the S_N2-type ring-opening chlorination and bromination of epoxides. Inclusion of alkoxy substituents on 6-B-3[17] fluoroboranes is known to decrease their Lewis acidity, and for example the fluoride affinities of a range of (methoxy)(fluoro)boranes have been shown to be: $(MeO)_3B < (MeO)_2BF < BF_3$,[26] although ring-opening fluorination reactions of epoxides using modified fluoroborane reagents are conspicuous by their paucity in the literature.[27] Nonetheless, the efficient ring-opening fluorination of epoxides such as **1** with 0.33 equiv of $BF_3{\cdot}OEt_2$ implies that the putative alkoxydifluoroborane [$ROBF_2$] and dialkoxyfluoroborane [$(RO)_2BF$] intermediates formed during this process transfer fluoride in preference to their alkoxy group(s). Building on this hypothesis, we resolved to investigate the ability of a range of alkoxy-substituted fluoroborane reagents to facilitate the successful ring-opening fluorination of *trans*-β-methyl-substituted aryl epoxides. We report herein our findings within this area, which culminate in the identification of pinacolatoboron fluoride (pinBF) as an efficient fluoride donor for this stereoselective ring-opening fluorination reaction.

As with alkoxy-substituted chloro- and bromoboranes, alkoxydifluoroboranes [$ROBF_2$] and dialkoxyfluoroboranes [$(RO)_2BF$] have previously been prepared by a redistribution process involving the treatment of $B(OR)_3$ with BF_3 or $BF_3{\cdot}OEt_2$ (in the appropriate stoichiometry), followed by distillation.[28,29] Encouraged by this precedent, and with the development of an operationally simple protocol in mind, a variety of $B(OR)_3$ additives, bearing alkoxy groups with increasing steric demand, were screened to assess their efficacy at promoting ring-opening fluorination of epoxide **2** in conjunction with $BF_3{\cdot}OEt_2$. In each case, the requisite fluorinating agent was prepared in a separate reaction vessel by pre-mixing the requisite amount of $B(OR)_3$ with 0.35 equiv of $BF_3{\cdot}OEt_2$ (i.e., giving 1.05 equiv of fluoride ion available for reaction in each case) in CH_2Cl_2 for 5 min at rt.[12] The resultant mixture was then added to a solution of epoxide **2** in CH_2Cl_2 at −20 °C for 5 min, then quenched by the addition of satd aq $NaHCO_3$ (i.e., analogous to the conditions that we have previously employed to effect the ring-opening fluorination of *trans*-β-substituted aryl epoxides using $BF_3{\cdot}OEt_2$ alone),[12] and the product distribution was then analysed by ^1H NMR spectroscopy. These reactions all gave rise to mixtures of products, of which the three main components were identified as fluorohydrin **8**, ketone **12** and the corresponding ether **13** (it being crucial that there was no evidence of fluorohydrin **8** in either the ^1H or ^{19}F NMR spectra of the crude product mixture of the analogous reaction employing $BF_3{\cdot}OEt_2$ alone). It was noted that integration of the resonance associated with the C(1)*H* proton (i.e., C*H*F) within fluorohydrin **8** at δ_H 5.12 ppm (1H, dd, *J* 48.1, 7.3) against the combined ArCH_3 resonances associated with all compounds present in the mixture (collection of singlet resonances at δ_H ~2.3–2.4 ppm) allowed quantification of the amount of fluorohydrin **8** in the mixture ('NMR yield') which gave excellent correlation with the isolated yield of fluorohydrin **8**. For example, treatment of epoxide **2** (92:8 dr) with a 2:1 mixture of $BF_3{\cdot}OEt_2$ and $B(OMe)_3$ (0.35 equiv and 0.18 equiv, respectively) gave fluorohydrin **8**, ketone **12,** and ether **13a** in the ratio of 28:34:38, respectively; chromatographic purification provided **8** in 22% yield (>95:5 dr), **12** in 26% yield, and **13a** in 31% yield (>95:5 dr). The relative *syn*-configuration within fluorohydrin **8** was assigned from the diagnostic value of the ^1H NMR ^3J coupling constant between C(1)*H* and C(2)*H* ($^3J_{1,2}$ = 7.3 Hz),[12] but the relative configuration within ether **13a** was not assigned.[30] The relative *syn*-configuration within **8** is also consistent with the stereochemical outcome of the ring-opening fluorination of related *trans*-β-substituted aryl epoxides with $BF_3{\cdot}OEt_2$ that we have previously reported:[12] the stereochemical outcome of this process has been unambiguously established by single crystal X-ray diffraction analysis in several cases (including that of **1** giving **7**).[12] Increasing the quantity of $BF_3{\cdot}OEt_2$ and $B(OMe)_3$ (to 0.70 and 0.35 equiv, respectively) in an effort to promote the ring-opening fluorination reaction in fact led to production of a *decreased* amount of fluorohydrin **8**: under these conditions a 5:49:46 mixture of **8**, **12** and **13a**, respectively, was produced. Of all the conditions examined, the use of 0.70 equiv of $B(O^iPr)_3$ and 0.35 equiv of $BF_3{\cdot}OEt_2$ [i.e., 1.05 equiv of the putative $(^iPrO)_2BF$ complex] proved the most efficacious, and delivered a 53:28:19 mixture of fluorohydrin **8**, ketone **12** and ether **13c**, from which **8** was isolated in 41% yield and >95:5 dr. Attempted optimisation of the temperature of this reaction did not prove particularly fruitful: between −50 °C and 10 °C, increasing the temperature in 10 °C intervals, gave a maximum 46% 'NMR yield' of fluorohydrin **8** when the reaction was conducted at −10 °C, although a significant decrease in the conversion to **8** (only 3% 'NMR yield') was noted when the reaction was run at 10 °C (Scheme 2).

In an effort to suppress unwanted alkoxy transfer competing with the desired fluoride transfer, the efficacy of cyclic B(2)-fluoro-1,3-dioxa-2-boracycles as fluorinating agents was next explored. B-Chloro-1,3-dioxa-2-boracyclopentane,[31,32] B-chloro-4,4,5,5-tetramethyl-1,3-dioxa-2-boracyclopentane (pinBCl)[33] and B-chloro-1,3-dioxa-2-boracyclohexane[34] have previously been prepared by treatment of the corresponding diols with BCl_3, although the analogous preparation of the fluorine analogues has not been reported. In the event, initial attempts at the use of this protocol with $BF_3{\cdot}OEt_2$ were not successful, and therefore an alternative was sought. Aldridge and co-workers have pioneered a convenient metathesis approach to alkoxy-substituted fluoroboranes, in which trimethylsilyl ethers serve as latent B-alkoxy ligands,[35] and a variant of this approach has also been demonstrated by Yamamoto and co-workers to access a B-ethynyl boronic ester.[36] Encouraged by this precedent, a range of bis(*O*-trimethylsilyl) ethers **14**–**20** were prepared by disilylation of the corresponding



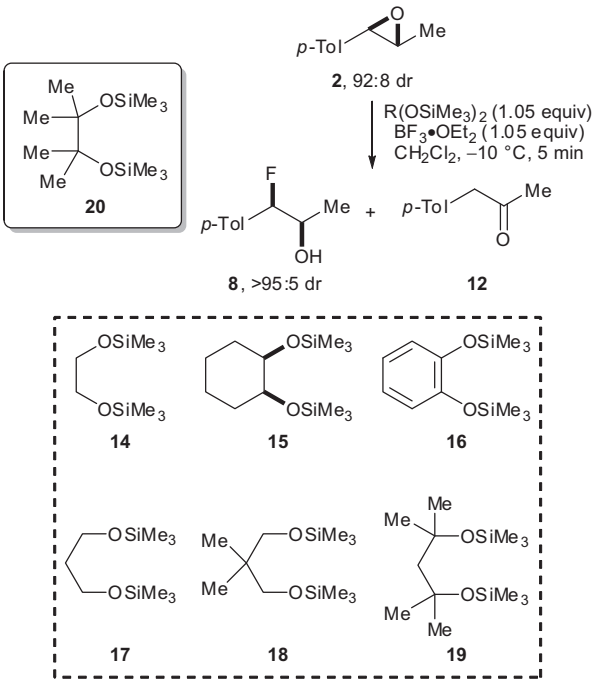
Putative fluoride source (equiv)	Ratio 8 : 12: 13	Fluorohydrin 8 Yield (NMR Yield)[a]	Ketone 12 Yield
$MeOBF_2$ (0.53)	28 : 34 : 38	22% (22%)	26%
$EtOBF_2$ (0.53)	28 : 35 : 37	23% (23%)	28%
$^{i}PrOBF_2$ (0.53)	44: 45 : 11	30% (30%)	27%
$^{t}BuOBF_2$ (0.53)[b]	22 : 78 : 0	(11%)	–
$(MeO)_2BF$ (1.05)	21 : 21 : 58	(15%)	–
$(EtO)_2BF$ (1.05)	30 : 16 : 54	(26%)	–
$(^{i}PrO)_2BF$ (1.05)	53 : 28 : 19	41% (39%)	–
$(^{t}BuO)_2BF$ (1.05)[b]	18 : 33 : 49	<15%[c] (12%)	–

Scheme 2. *p*-Tol = *para*-tolyl. [a]The 'NMR yield' was calculated by integration of the C*H*F resonance against the combined ArCH_3 resonances in the ^{1}H NMR spectrum of the crude product mixture. [b]On pre-mixing $BF_3{\cdot}OEt_2$ and $B(O^tBu)_3$, some gelatinous material was formed that proved insoluble in CH_2Cl_2, and this material was not transferred into the reaction vessel containing the epoxide. [c]An impure sample of **8** was isolated.

diols with Me_3SiCl. Subsequently, 1.05 equiv of **14–20** was then mixed with 1.05 equiv of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 for 5 min at rt. The resultant mixture was then added to a solution of epoxide **2** in CH_2Cl_2 at −10 °C.[37] Each of these reactions produced fluorohydrin **8** and ketone **12**, in addition to other unidentified products, and an 'NMR yield' was calculated for **8**. This proved to be low to modest (⩽36%) in all of the cases examined with the exception of the reaction using bis(*O*-trimethylsilyl)pinacol **20**, which gave **8** in 56% 'NMR yield'. Purification of this mixture allowed isolation of **8** in 57% yield and >95:5 dr (Scheme 3).

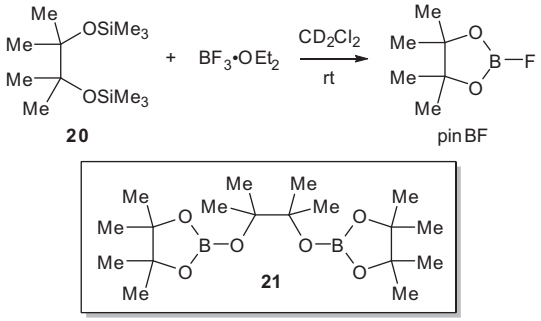
On mixing $BF_3{\cdot}OEt_2$ and bis(*O*-trimethylsilyl)pinacol **20** in CD_2Cl_2 at rt, a colourless solution containing a small amount of an unidentified white precipitate was produced. The solution was decanted and analysed by ^{1}H, ^{11}B, ^{13}C and ^{19}F NMR spectroscopy, which showed only trace amounts (<1%) of both $BF_3{\cdot}OEt_2$ and **20** remaining, the presence of Me_3SiF and one other fluorine-containing species, assigned as pinBF (δ_B 20.6 ppm;[38] δ_F −152 ppm),[39,40] alongside one other identifiable species, tentatively assigned as bis(*O*-pinacolatoboryl)pinacol **21**.[41] The yield of pinBF was estimated at 60% based on integration of its tetramethyl resonance in the ^{1}H NMR spectrum (at δ_H 1.34 ppm) against the combined methyl resonances present for all compounds in the mixture (collection of singlet resonances at δ_H 1.25–1.40 ppm). If this represents an accurate quantification of the amount of active fluorinating agent generated in this manner, it may account for the moderate yield (57%) of fluorohydrin **8** obtained from the treatment of epoxide **2** with in situ generated pinBF. Unfortunately, attempts to improve the yield of **8** by increasing the amount of pinBF promoted formation of ketone **12** at the expense of **8**, and several attempts to isolate pinBF via distillation proved unsuccessful (Scheme 4).

Having established that pinBF is an efficient fluorinating agent for epoxide **2**, the effect of the reaction temperature on the yield



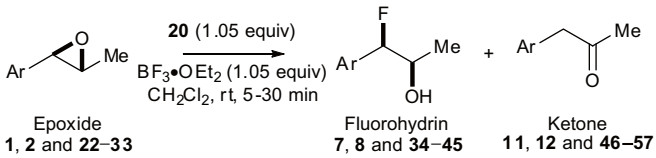
Bis-*O*TMS-ether	Ratio 8 : 12	Fluorohydrin 8 Yield (NMR yield)[a]
14	17 : 83	(6%)
15	29 : 71	(15%)
16	19 : 81	(5%)
17	66 : 34	(36%)
18	57 : 43	(36%)
19	40 : 60 [b]	(7%)
20	72 : 28	57% (56%)

Scheme 3. *p*-Tol = *para*-tolyl. [a]The 'NMR yield' was calculated by integration of the C*H*F resonance against the combined ArCH_3 resonances in the ^{1}H NMR spectrum of the crude product mixture. [b]22% conversion.



Scheme 4.

of fluorohydrin **8** was evaluated (range from −50 °C to 30 °C), with reaction at room temperature (20–25 °C) proving marginally superior (and operationally more facile), furnishing a 77:23 mixture of fluorohydrin **8** and ketone **12**, from which **8** was isolated in 59% yield and >95:5 dr.[42] With an optimal procedure in hand, the generality of this approach across a number of *trans*-β-methyl-substituted aryl epoxides **1** and **22–33** was next assessed (Scheme 5);[43] this range was chosen so that the effect of the electronic nature of the aryl groups (with associated Brown–Okamoto σ^+ substituent



	Ar	σ+	Epoxide dr	Time (min)	Product(s), ratio	Fluorohydrin Yield (dr)	$^3J_{1,2}$ Hz	Ketone Yield
	p-$MeOC_6H_4$	−0.78	**22**, 96:4 dr	5	**34**:**46**, 0:100	**34**, –	–	**46**, 69%
	p-$PhOC_6H_4$	−0.50	**23**, 96:4 dr	5	**35**:**47**, 0:100	**35**, –	–	**47**, 78%
Substrate scope with pinBF	*p*-MeC_6H_4	−0.31	**2**, 90:10 dr	5	**8**:**12**, 77:23	**8**, 59% (>95:5 dr)	7.3	**12**, not isolated
Substrate scope with pinBF	*p*-PhC_6H_4	−0.18	**24**, 98:2 dr	5	**36**:**48**, 70:30	**36**, 53% (>95:5 dr)	7.1	**48**, 25%
Substrate scope with pinBF	2-naphthyl	−0.13	**25**, 96:4 dr	5	**37**:**49**, 73:27	**37**, 56% (>95:5 dr)	7.1	**49**, 22%
Substrate scope with BF_3·OEt_2	*p*-FC_6H_4	−0.07	**26**, 94:6 dr	5	**38**:**50**, 77:23	**38**, 52% (>95:5 dr)	7.2	**50**, 10%
Substrate scope with BF_3·OEt_2	Ph	0.00	**1**, >99:1 dr	5	**7**:**11**, 81:19	**7**, 63% (98:2 dr)	7.1	**11**, not isolated
Substrate scope with BF_3·OEt_2	*m*-$MeOC_6H_4$	+0.05	**27**, 93:7 dr	5	**39**:**51**, 66:34	**39**, 54% (>95:5 dr)	7.0	**51**, not isolated
Substrate scope with BF_3·OEt_2	*p*-ClC_6H_4	+0.11	**28**, 94:6 dr	10	**40**:**52**, 68:32	**40**, 57% (>95:5 dr)	7.0	**52**, 27%
Substrate scope with BF_3·OEt_2	*p*-BrC_6H_4	+0.15	**29**, 94:6 dr	10	**41**:**53**, 62:38	**41**, 54% (>95:5 dr)	6.8	**53**, 31%
Substrate scope with BF_3·OEt_2	*m*-FC_6H_4	+0.35	**30**, 95:5 dr	15	**42**:**54**, 72:28	**42**, 55% (90:10 dr)	6.8 (4.6)[a]	**54**, 22%
Substrate scope with BF_3·OEt_2	*m*-ClC_6H_4	+0.40	**31**, 92:8 dr	15	**43**:**55**, 74:26	**43**, 56% (89:11 dr)	6.7 (4.6)[a]	**55**, 23%
Substrate scope with BF_3·OEt_2	*m*-BrC_6H_4	+0.41	**32**, 91:9 dr	15	**44**:**56**, 71:29	**44**, 51% (88:12 dr)	6.6 (4.8)[a]	**56**, 20%
	p-$CF_3C_6H_4$	+0.61	**33**, 94:6 dr	30	no reaction	**45**, –	–	**57**, –

Scheme 5. [a]The associated coupling constant for the minor diastereoisomer (where formed) is shown in parentheses.

constants ranging from −0.78 to +0.61)[44] on the efficacy of this procedure could be investigated, and a direct comparison of substrate scope when employing BF_3·OEt_2 alone could be made.[12] Consistent with our previous investigations using BF_3·OEt_2 alone,[12] reaction of the very electron-rich species **22** (Ar = *p*-$MeOC_6H_4$) and **23** (*p*-$PhOC_6H_4$) with pinBF gave the corresponding arylpropan-2-ones **46** and **47** as major products, which were isolated in 69% and 78% yields, respectively. No trace of the corresponding fluorohydrins **34** and **35** was apparent by ^{1}H and ^{19}F NMR spectroscopic analyses of the crude product mixtures. In contrast to the results using BF_3·OEt_2 alone,[12] however, ring-opening fluorination of the modestly electron-rich species **24** (Ar = *p*-PhC_6H_4) and **25** (Ar = 2-naphthyl) upon treatment with pinBF gave the corresponding fluorohydrins **36** and **37** as the major products, which were isolated in 53% and 56% yields, respectively, and in >95:5 dr in both cases. The relative *syn*-configuration within fluorohydrin **36** (Ar = *p*-PhC_6H_4) was established unambiguously by single crystal X-ray diffraction analysis (Figure 1).[45] This analysis also supports our initial configurational assignment of fluorohydrin **8**, and allowed the relative *syn*-configuration within **37** to be confidently assigned from the diagnostic values of the ^{1}H NMR ^3J coupling constant between C(1)*H* and C(2)*H* (7.1 Hz in both cases). The remaining substrates **1** and **26**–**33** when treated with pinBF revealed similar behaviour to the corresponding reactions employing BF_3·OEt_2 alone.[12] Reaction of epoxides **26** (Ar = *p*-FC_6H_4), **1** (Ar = Ph) and **27** (Ar = *m*-$MeOC_6H_4$) with pinBF gave complete conversion to the corresponding fluorohydrins **38**, **7** and **39** within 5 min, which were isolated in 52%, 63% and 54% yields, respectively, and >95:5 dr in each case, whilst reaction of the more electron-deficient species **28** (Ar = *p*-ClC_6H_4) and **29** (Ar = *p*-BrC_6H_4) required a reaction time of 10 min to give fluorohydrins **40** and **41** (57% and 54% isolated yields, respectively, and >95:5 dr in both cases). Meanwhile, treatment of epoxides **30** (Ar = *m*-FC_6H_4), **31** (Ar = *m*-ClC_6H_4) and **32** (Ar = *m*-BrC_6H_4) with pinBF required 15 min for complete consumption of starting material, and gave the corresponding fluorohydrins **42**–**44** in ~90:10 dr in each case, consistent with an apparent erosion of the diastereoselectivity of the fluorination process. This may suggest a competing S_N2-type ring-opening occurs in these cases, which has previously been observed during the formation of fluorohydrin products from very electron-poor aryl epoxides upon treatment with BF_3·OEt_2.[46] Finally, reaction of **33** (Ar = *p*-$CF_3C_6H_4$) with pinBF resulted in no reaction, and returned only starting material (Scheme 5).

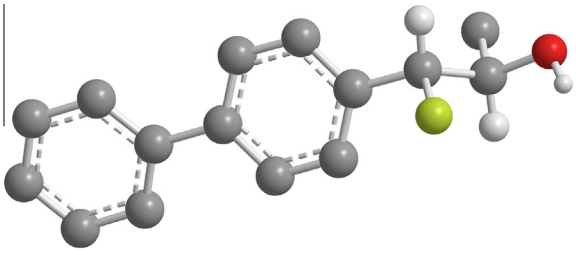


Figure 1. X-ray crystal structure of **36** (selected H atoms are omitted for clarity).

In conclusion, treatment of a range of *trans*-β-methyl-substituted aryl epoxides with pinacolatoboron fluoride (pinBF), generated in situ from BF_3·OEt_2 and bis(*O*-trimethylsilyl)pinacol, results in highly stereoselective S_N1-type epoxide ring-opening to give the corresponding *syn*-fluorohydrins. This operationally-simple protocol, which benefits from short reaction time at ambient temperature, allows access to stereodefined benzylic fluoride building blocks (the hydroxyl functionality within these building blocks being an ideal synthetic handle for conversion to a range of other functionality). The substrate scope of this reaction includes those epoxides bearing relatively electron-rich aryl groups, which fail to deliver fluorohydrins using BF_3·OEt_2 alone as the fluorinating agent.

Acknowledgments

The authors would like to thank Syngenta for a CASE studentship (A.J.C.), the European Comission for an Erasmus Scholarship (D.H.), and the Department of Organic Chemistry, University of Groningen for H. J. Backer-fonds (D.H.).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.044.

References and notes

1. For example, see: (a) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013; (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320; (c) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071.
2. For example, see: (a) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3; (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.
3. Murray, T. K.; Whalley, K.; Robinson, C. S.; Ward, M. A.; Hicks, C. A.; Caroline, A.; Lodge, D.; Vandergriff, J. L.; Baumbarger, P.; Siuda, E.; Gates, M.; Ogden, A. M. *J. Pharmacol. Exp. Ther.* **2003**, *306*, 752.
4. Bio, M. M.; Waters, M.; Javadi, G.; Song, Z. J.; Zhang, F.; Thomas, D. *Synthesis* **2008**, 891.
5. Paulsen, H.; Antons, S.; Brandes, A.; Lögers, M.; Müller, S. N.; Naab, P.; Schmeck, C.; Schneider, S.; Stoltefuß, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3373.
6. Huang, H.; Han, W.-G.; Noodleman, L.; Grynszpan, F. *Bioorg. Med. Chem.* **2001**, *9*, 3185.
7. Walba, D. M.; Razavi, H. A.; Clark, N. A.; Parmar, D. S. *J. Am. Chem. Soc.* **1988**, *110*, 8686.
8. For reviews , see: (a) Gerstenberger, M. R. C.; Haas, A. *Angew. Chem., Int. Ed.* **1981**, *20*, 647; (b) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505; (c) Mascaretti, O. A. *Aldrichim. Acta* **1993**, *26*, 47; (d) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discov. Dev.* **2008**, *11*, 803.
9. For a review on asymmetric fluorination, see: (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, 108; PR1. For a review focusing on catalytic asymmetric fluorination, see: (b) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065.
10. Murthy, A. S. K.; Tardivel, R.; Grée, R. Product Subclass 6: Benzylic Fluorides. In *Science of Synthesis*; Percy, J., Ed.; Fluorine; Thieme: Stuttgart, 2006; Vol. 34, p 295.
11. For selected examples of the asymmetric synthesis of benzylic fluorides not reliant on nucleophilic fluorination see: (a) Grée, D.; Grée, R. *Tetrahedron Lett.* **2007**, *48*, 5435; (b) García Ruano, J. L.; Parra, A.; Alonso, I.; Fustero, S.; del Pozo, C.; Arroyo, Y.; Sanz-Tejedor, A. *Chem.-Eur. J.* **2011**, *17*, 6142.
12. Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Tyte, M. J. *Org. Lett.* **2010**, *12*, 2936.
13. Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Morris, M. J.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2011**, *76*, 4617.
14. Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; Tyte, M. J. *J. Org. Chem.* **2012**, *77*, 7262.
15. Cresswell, A. J.; Davies, S. G.; Hewings, D. S.; Kurosawa, W.; Lee, J. A.; Morris, M. J.; Roberts, P. M.; Thomson, J. E. *J. Chem. Crystallogr.* **2013**, *43*, 646.
16. For a fully comprehensive (up to the end of 2013) review of this approach, see: Cresswell, A. J.; Davies, S. G.; Roberts, P. M.; Thomson, J. E. *Chem. Rev.* **2015**. http://dx.doi.org/10.1021/cr5001805; For more recent reports in this area, see: (a) Roscales, S.; Csákÿ, A. G. *Chem. Commun.* **2014**, 454; (b) Yang, T.-P.; Li, Q.; Lin, J.-H.; Xiao, J.-C. *Chem. Commun.* **2014**, 1077; (c) Cui, J.; Jia, Q.; Feng, R.-Z.; Liu, S.-S.; He, T.; Zhang, C. *Org. Lett.* **2014**, *16*, 1442.
17. The N–X–L descriptors were introduced by Martin and co-workers to designate the bonding about any atom (X) in a resonance structure in terms of the number of valence shell electrons (N) formally associated directly with that atom and the number of ligands (L) directly bonded to it; see: Perkins, C. W.; Martin, J. C.; Arduengo, A. J.; Lau, W.; Alegria, A.; Kochi, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 7753.
18. Vianello, R.; Maksić, Z. *Inorg. Chem.* **2005**, *44*, 1095.
19. Grant, D. J.; Dixon, D. A. *Inorg. Chem.* **2009**, *48*, 8811.
20. (a) Bovicelli, P.; Mincione, E.; Ortaggi, G. *Tetrahedron Lett.* **1991**, *32*, 3719; (b) Bovicelli, P.; Lupattelli, P.; Bersani, M. T. *Tetrahedron Lett.* **1992**, *33*, 6181; (c) Brown, H. C.; Roy, C. D. *Mol. Online* **1998**, *2*, 114; (d) Roy, C. D.; Brown, H. C. *Aust. J. Chem.* **2007**, *60*, 139; (e) Roy, C. D.; Brown, H. C. *J. Organomet. Chem.* **2007**, *692*, 1608.
21. (a) Guindon, Y.; Yoakim, C.; Morton, H. E. *Tetrahedron Lett.* **1983**, *24*, 2969; (b) Guindon, Y.; Anderson, P. C.; Yoakim, C.; Girard, Y.; Berthiaume, S.; Morton, H. E. *Pure Appl. Chem.* **1988**, *60*, 1705; (c) Roy, C. D.; Brown, H. C. *Aust. J. Chem.* **2006**, *59*, 657.
22. Bell, T. W.; Ciaccio, J. A. *Tetrahedron Lett.* **1986**, *27*, 827.
23. Guindon, Y.; Therien, M.; Girard, Y.; Yoskim, C. *J. Org. Chem.* **1987**, *52*, 1680.
24. Roy, C. D.; Brown, H. C. *Aust. J. Chem.* **2006**, *59*, 834.
25. Roy, C. D.; Brown, H. C. *J. Chem. Res.* **2006**, 639.
26. Larson, J. W.; McMahon, T. B. *J. Am. Chem. Soc.* **1985**, *107*, 766.
27. Bruns, S.; Haufe, G. *J. Fluorine Chem.* **2000**, *104*, 247; Bruns and Haufe have attempted ring-opening fluorination of cyclohexene oxide using Ipc_2BF, although cyclohexanone was formed as the major product with no fluorohydrin detected; see: Morra, N. A.; Pagenkopf, B. L. *Eur. J. Org. Chem.* **2013**, 756.
28. For the preparation of alkoxydifluoroboranes $ROBF_2$ see: (a) Gerrard, W.; Mooney, E. F.; Peterson, W. G. *J. Inorg. Nucl. Chem.* **1967**, *29*, 943; For the preparation of dialkoxyfluoroboranes $(RO)_2BF$ see: (b) Cook, H. C.; Ilett, J. O.; Saunders, B. C.; Starey, G. J. *J. Chem. Soc.* **1950**, 3126; (c) Rauchschwalbe, G.; Schlosser, M. *Helv. Chim. Acta* **1975**, *58*, 1094; It has been reported that $(RO)_2BF$ is unstable with respect to (slow) disproportionation into $ROBF_2$ and $B(OR)_3$; see: (d) Wiberg, E.; Sütterlin, W. Z. *Anorg. Chem.* **1931**, *202*, 22.
29. On the basis of ^{11}B NMR, Raman and IR spectroscopy, alkoxydifluoroboranes $ROBF_2$ are believed to exist entirely as trimers $(ROBF_2)_3$ in both the neat liquid and in benzene solution; see: (a) de Moor, J. E.; van der Kelen, G. P. *J. Organomet. Chem.* **1966**, *6*, 235; Rasul and Williams showed that $(MeOBF_2)_3$ is the thermodynamic product when $B(OMe)_3$ and BF_3 are mixed in a 1:2 ratio; see: (b) Rasul, G.; Williams, R. E. *Collect. Czech. Chem. Commun.* **1999**, *64*, 847. For the sake of simplicity, in this manuscript, all alkoxydifluoroboranes are denoted by their empirical formula $ROBF_2$.
30. Ring-opening aryloxylation of aryl epoxides with $B(OAr)_3$ reagents is known to be highly *syn*-selective; see:(a) Pineschi, M.; Bertolini, F.; Haak, R. M.; Crotti, P.; Macchia, F. *Chem. Commun.* **2005**, 1426; (b) Bertolini, F.; Crotti, P.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **2006**, *47*, 61.
31. Gennari, C.; Colombo, L.; Poli, G. *Tetrahedron Lett.* **1984**, *25*, 2279.
32. Blau, J. A.; Gerrard, W.; Lappert, M. F. *J. Chem. Soc.* **1957**, 4116.
33. Bettinger, H. F.; Filthaus, M.; Bornemann, H.; Oppel, I. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4744.
34. Finch, A.; Lockhart, J. C.; Pearn, J. *J. Org. Chem.* **1961**, *26*, 3250.
35. Aldridge, S.; Calder, R. J.; Coombs, D. L.; Jones, C.; Steed, J. W.; Coles, S.; Hursthouse, M. B. *New J. Chem.* **2002**, *26*, 677.
36. Yamamoto, Y.; Hattori, K.; Ishii, J.-I.; Nishiyama, H. *Tetrahedron* **2006**, *62*, 4294.
37. In some cases, a small amount of a white precipitate formed, and this was also transferred to the reaction flask containing **2**.
38. The resonance at δ_B 20.6 ppm (attributed to the presence of pinBF) is within the expected range for sp^2-hybridised boron (~30 ppm) rather than sp^3-hybridised boron (~0 ppm) and is therefore indicative of a free Lewis acid rather than a complex with the Et_2O present in the mixture; see: Egawa, Y.; Gotoh, R.; Niina, S.; Anzai, J.-I. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3789.
39. A ^{10}B satellite peak was also observed slightly upfield due to a $^2\Delta^{19}F(^{10/11}B)$ isotope-induced chemical shift effect; see: Tordeaux, M.; Magnier, E.; Guidotti, J.; Diter, P.; Wakselman, C. *Magn. Reson. Chem.* **2004**, *42*, 700.
40. Braun, T.; Salomon, M. A.; Altenhöner, K.; Teltewskoi, M.; Hinze, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 1818. We would like to thank Professor Braun and Michael Teltewskoi for their ^{11}B and ^{19}F NMR spectroscopic data for their sample of pinBF (prepared from $Et_3N{\cdot}3HF$ and pinBH).
41. Analogously, diethylene ethylene di(borate) has been reported as a by-product during the synthesis of ethylene chloroboronate from BCl_3 and ethylene glycol; see Ref. 32.
42. Use of 2 equiv of $BF_3{\cdot}OEt_2$ and 2 equiv of bis(*O*-trimethylsilyl)pinacol **20** to promote the formation of fluorohydrin **8** gave inferior results in this reaction, and gave ketone **10** as the major product.
43. $BF_3{\cdot}OEt_2$ (90.7 μL, 0.74 mmol, 1.05 equiv) was added in one portion to a stirred solution of **20** (193 mg, 0.74 mmol, 1.05 equiv) in CH_2Cl_2 (1.40 mL) under N_2 at rt, and the resultant mixture was stirred at rt for 5 min. The solution was then transferred via a syringe to a stirred solution of the requisite epoxide (0.70 mmol, 1 equiv) in CH_2Cl_2 (1.40 mL) at rt under a N_2 atmosphere, and the resultant mixture was stirred at rt for 5–15 min. Satd aq $NaHCO_3$ (5 mL) was then added and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 5 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried and concentrated in vacuo.
44. Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.
45. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 864777.
46. Barili, P. L.; Bellucci, G.; Berti, G.; Macchia, B.; Macchia, F. *J. Chem. Soc., Perkin Trans. 1* **1974**, 477.