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An *In Situ* Directing Group Strategy for Chiral Anion Phase-Transfer Fluorination of Allylic Alcohols

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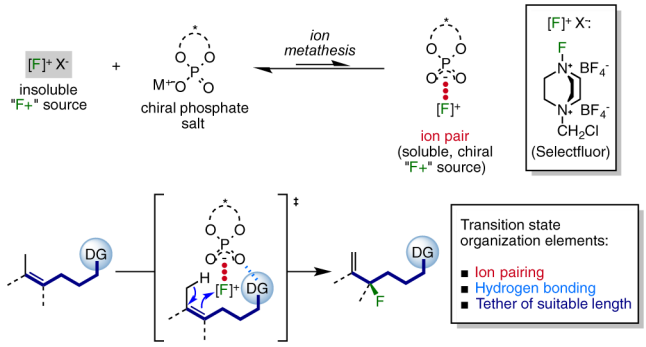
Supporting Information

ABSTRACT: An enantioselective fluorination of allylic alcohols under chiral anion phase-transfer conditions is reported. The *in situ* generation of a directing group proved crucial for achieving effective enantiocontrol. In the presence of such a directing group, a range of acyclic substrates underwent fluorination to afford highly enantioenriched α-fluoro homoallylic alcohols. Mechanistic studies suggest that this transformation proceeds through a concerted enantiodetermining transition state involving both C−F bond formation and C−H bond cleavage.

Despite the unique importance of fluorine in biologically active compounds, the catalytic enantioselective introduction of stereogenic fluorine substituents remains a challenging synthetic transformation.[1] Although fluoride is readily available and atom-economical, the use of F^- in asymmetric catalysis is an inherently demanding task, and nucleophilic fluorination has only recently been realized through the development of transition metal-based catalytic systems.[2] The complementary approach of using electrophilic reagents for the fluorination of nucleophilic carbon centers has been more broadly applicable, in part due to the commercial availability of N−F reagents covering a broad range of reactivity. Several distinct strategies have been advanced to achieve asymmetric induction using electrophilic fluorinating reagents, including enamine catalysis,[3a−e] nucleophilic catalysis,[3f,g] cationic phase-transfer catalysis,[3h−j] Lewis acid activation of 1,3-dicarbonyl compounds,[3k−m] transfer fluorination using chiral tertiary amines,[3n−q] and late transition metal-catalyzed π-activation of olefins.[3r] With the exception of olefin π-activation, these strategies generally employ activation modes requiring electron-rich olefins (allylsilanes, metal enolates, silyl enol ethers, enamines, or π-excessive heterocycles) as substrates or reactive intermediates. Hence, only a few examples of the enantioselective fluorination of unactivated or weakly activated alkenes have been reported.[4]

Our group has developed *chiral anion phase-transfer catalysis* as a general approach for asymmetric synthesis involving cationic reagents or intermediates.[5] The application of this approach to enantioselective fluorination has been achieved using Selectfluor, an ionic electrophilic reagent otherwise insoluble and unreactive in nonpolar media, which is activated through ion-exchange with a catalytic amount of a lipophilc chiral phosphate salt (Scheme 1, top). The resulting chiral ion pair serves as the active electrophilic species in solution, allowing for the fluorination of olefin starting materials in an enantioselective manner. As a consequence of this mode of activation, unselective background reactivity is minimal, despite the large excess of bulk reagent relative to catalyst and the high intrinsic reactivity of Selectfluor. Notably, alkenes without activating heteroatomic substituents can be fluorinated, suggesting that this approach may prove applicable to the preparation of fundamental yet synthetically formidable chiral fluorinated building blocks directly from readily available olefins.

Scheme 1. Directed Fluorination via Chiral Anion Phase-Transfer Catalysis



We were particularly intrigued by our recent discovery that a carboxamide or phenol group at the allylic position of an alkene could direct the fluorination of the double bond to deliver the fluorination−elimination product with excellent enantioselectivity (Scheme 1, bottom).[6,7] The scope of this methodology, however, was limited to relatively specialized substrates bearing ring fusions or pendent phenols, and we were interested in advancing this methodology toward more fundamental and versatile substrates. In particular, we directed our attention to allylic alcohols as a general and easily accessible class of substrates, conjecturing that the hydroxyl group would direct enantioselective fluorination. In initial studies, however, subjecting cinnamyl alcohol **1a** to the previously established fluorination conditions provided fluorinated product with essentially no enantiocontrol (eq 1).

Previously,[6] we observed that length of the spacer between the directing group and alkene was important for achieving effective directed fluorination, with high enantioselectivities attained when the double bond is δ to the terminus of the directing group. Speculating that the hydroxyl group of the allylic alcohol was too close to the alkene to serve as a directing group, we sought to lengthen the spacer using a readily removed auxiliary group. A report by Falck and co-workers describing the use of boronic

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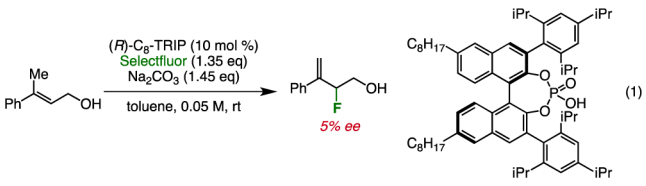
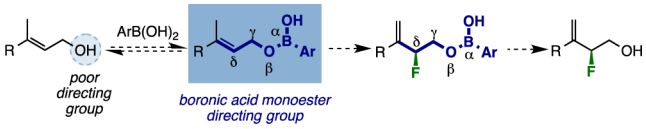


acids to effect a formal enantioselective conjugate addition of hydroxide inspired us to consider the use of boronic acid monoesters as directing groups.[8,9] The geometric analogy between our previously successful directing groups and the boronic acid monoester led us to suspect that the latter would be appropriately positioned relative to the alkene to be a competent directing group. In addition, the use of these boronic esters would provide the opportunity to fine-tune the acidity (and, thus, hydrogen-bonding properties) of the directing group, as well as its steric bulk, both of which previously proved crucial for obtaining high enantioselectivities.[6] Since boronic acid monoesters are readily formed by condensation of boronic acids and alcohols and also readily hydrolyzed, we postulated that such esters could function as *in situ directing groups* (Scheme 2). We

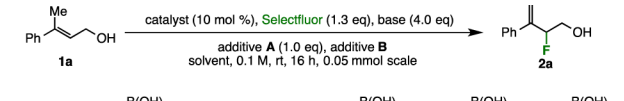
Scheme 2. Proposed Boronic Acid Monoester-Directed Transformation

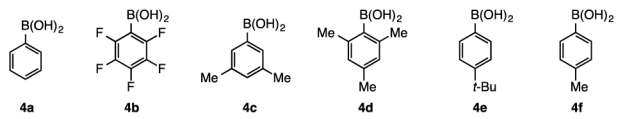


envisioned executing this strategy by using a stoichiometric boronic acid additive to generate the directing group, which would subsequently be removed upon chromatographic purification. In this Communication, we report the successful implementation of this tactic for the enantioselective fluorination of allylic alcohols, including substrates with little steric or electronic bias.

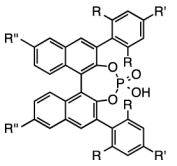
To probe the validity of our hypothesis, we first evaluated the effect of incorporating phenylboronic acid (1.0 equiv) as an additive under reaction conditions otherwise identical to the ones shown in eq 1. We were encouraged to observe a significant increase in enantioselectivity (Table 1, entry 1).[10,11] A thorough evaluation of commercially available boronic acids revealed that substituents on the boronic acid strongly influenced enantioselectivity (selected results shown in Table 1). For instance, the more acidic pentafluorophenylboronic acid (**4b**) delivered racemic product (entry 2). Moreover, the presence of methyl groups at the 3,5-positions resulted in the opposite sense of enantioinduction compared to unsubstituted phenylboronic acid, while 2,6-substitution inhibited reactivity (entries 3 and 4). *p*-Tolylboronic acid (**4f**) was found to be particularly effective and was chosen as the boronic acid for further optimization. We reasoned that enantioselectivity might be further improved by removal of water to shift the equilibrium in favor of boronic ester formation.[12] Indeed, the addition of 4Å molecular sieves resulted in a significant increase in enantioselectivity (entry 6 vs 7). Catalyst **3c** (**AdDIP**) bearing 4-(1-adamantyl)-2,6-diisopropyl substituents on the 3,3′ position of the BINOL scaffold was found to further enhance enantioselectivity (entry 9).[13] Finally, optimization of base (Na_2HPO_4) and fine-tuning of solvent and desiccant provided conditions to generate fluorinated product **2a** in high yield and excellent enantioselectivity (entry 13). Omitting the boronic acid under otherwise optimized conditions

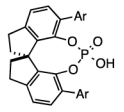
Table 1. Optimization of Reaction Conditions





entry	catalyst	base	solvent[a]	A	B	% ee[b,c] (conv.[d])
Effect of boronic acid						
1	(*R*)-**3a**	Na_2CO_3	toluene	**4a**	none	35 (98)
2	(*R*)-**3a**	Na_2CO_3	toluene	**4b**	none	0 (67)
3	(*R*)-**3a**	Na_2CO_3	toluene	**4c**	none	–30 (53)
4	(*R*)-**3a**	Na_2CO_3	toluene	**4d**	none	n.d. (6)
5	(*R*)-**3a**	Na_2CO_3	toluene	**4e**	none	25 (81)
6	(*R*)-**3a**	Na_2CO_3	toluene	**4f**	none	50 (97)
7	(*R*)-**3a**	Na_2CO_3	toluene	**4f**	4A MS	61 (88)
Catalyst evaluation						
8	(*R*)-**3b**	Na_2CO_3	toluene	**4f**	4A MS	56
9	(*S*)-**3c**	Na_2CO_3	toluene	**4f**	4A MS	–69
10	(*S*)-**3d**	Na_2CO_3	toluene	**4f**	4A MS	–57
Further optimization of base, solvent, and desiccant						
11	(*S*)-**3c**	Na_2HPO_4	toluene	**4f**	4A MS	–88
12	(*S*)-**3c**	Na_2HPO_4	*p*-xyl/EC	**4f**	4A MS	–90
13	(*S*)-**3c**	Na_2HPO_4	*p*-xyl/EC	**4f**	$MgSO_4$	–93[e] (96)
14	(*S*)-**3c**	Na_2HPO_4	*p*-xyl/EC	none	$MgSO_4$	4 (97)





[a] *p*-xyl/EC = *p*-xylene/ethylcyclohexane (1:1). [b] ee determined by chiral HPLC. [c] Negative sign indicates opposite sense of stereoinduction relative to entry 1. [d] Conversions determined by ^{1}H NMR of the crude reaction mixture. [e] On 0.1 mmol scale, in 72% isolated yield.

resulted in complete loss of enantiocontrol, underscoring the essentiality of this additive (entry 14).[14]

Under these optimized conditions, we explored the substrate scope of the transformation. Substrates bearing weakly electron-donating to moderately electron-withdrawing substituents at the *para* position furnished fluorinated product in good to excellent yields and enantioselectivities (entries 1−6). Substitution at the *meta* and *ortho* positions afforded products with diminished but still useful enantioselectivities (entries 7−11). Substituents larger than methyl at the α position of the aryl ring were tolerated, giving rise to fluorinated alcohols bearing trisubstituted double bonds with good E/Z selectivity and excellent enantioselectivity (entries 12 and 13). Finally, these conditions proved applicable to non-styrenyl allylic alcohols (entries 14 and 15). Notably, an allylic alcohol bearing methyl and primary alkyl substituents reacted to form the fluorinated product in high yield and good enantioselectivity (entry 15).[15]

We conducted kinetic isotope effect experiments to gain some understanding of the basic mechanistic features of this system. A significant isotope effect was found in both intra- and intermolecular experiments, with the values for k_H/k_D agreeing within experimental error (eqs 2a and 2b). The magnitude of the observed KIE exceeds that attributable to hyperconjugative stabilization of a carbocation, thus excluding a mechanism in which rate-determining formation of a discrete fluorinated carbocationic species occurs, followed by rapid loss of a proton (Scheme 3, pathway I).[16] On the other hand, these data are consistent with the involvement of C−H bond cleavage in an asynchronous rate-determining transition state, either in a one-step process or after initial reversible formation of an alkene−Selectfluor π-complex (pathway II).[17] In support of this interpretation, subjecting trideuterated substrate **1b**-d_3 to standard reaction conditions resulted in significantly diminished enantioselectivity (83% vs 93% ee) compared to unlabeled **1b**

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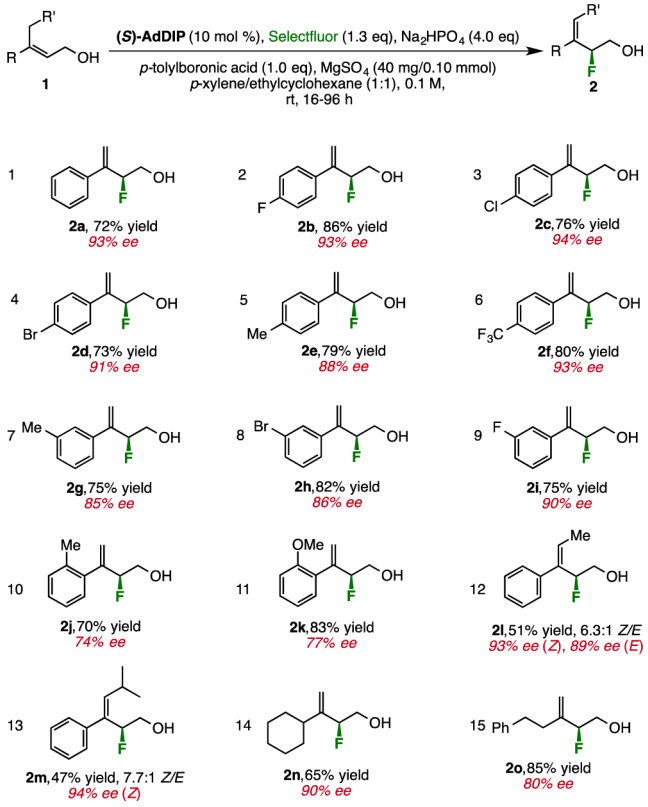
Table 2. Substrate Scope of the Enantioselective Fluorination of Allylic Alcohols[a]



[a]Absolute configurations assigned by analogy to that of **2d**, which was determined to be (*S*) by single-crystal X-ray diffraction (Figure 1).

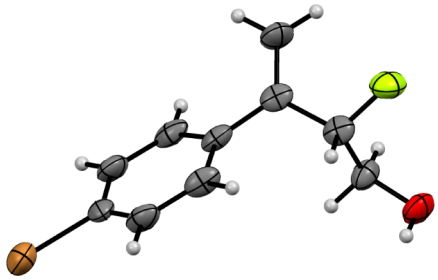
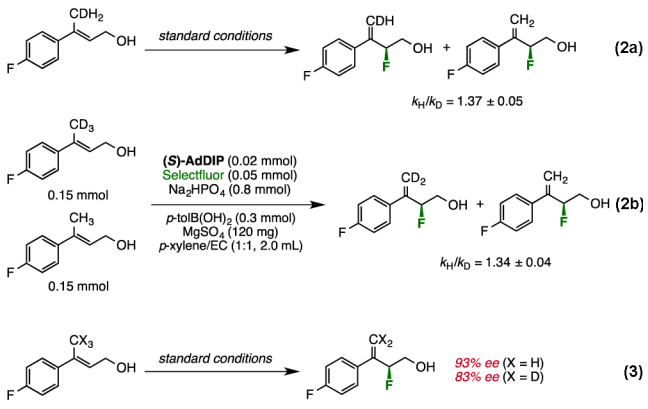
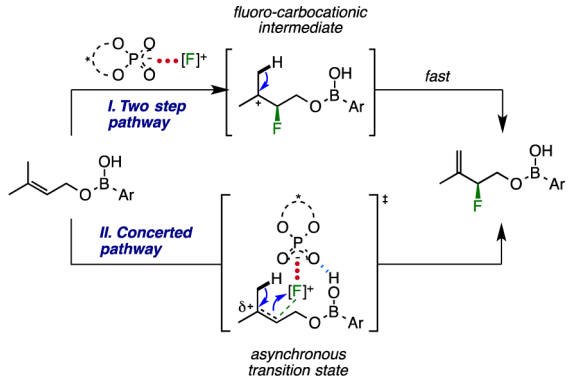


Figure 1. X-ray crystallographic structure of **2d** (ellipsoids at 50% probability).



(eq 3), implicating the cleavage of the C−H bond in the enantiodetermining step. In a broader context, while chiral acids have previously been utilized in reactions in which protonation is the enantiodetermining step,[18] these results suggest that in chiral anion catalysis, the microscopic reverse of this process (i.e., enantiodetermining deprotonation) may occur.

Scheme 3. Two Mechanistic Possibilities for the Boronic Acid-Mediated Enantioselective Fluorination−Elimination Reaction



In summary, we have shown that the generation of an *in situ* directing group, in conjunction with chiral anion phase-transfer catalysis, allows for the enantioselective fluorination of simple allylic alcohols. This approach significantly extends the scope of electrophilic enantioselective fluorination to unactivated and synthetically versatile substrates and potentially represents a general strategy for other substrate-directed reactions. In addition, mechanistic experiments suggest a process in which C−F bond formation and C−H bond cleavage occur in a concerted enantiodetermining transition state, with cleavage of the C−H bond playing an unusually significant role in asymmetric induction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) The use of substoichiometric (0.8 equiv) boronic acid resulted in reduced enantioselectivity, while the use of excess (2.0 equiv) had no additional benefit (see the Supporting Information).

(11) There is no clear correlation between observed reaction rates and enantioselectivity (see Table 1). We tentatively attribute this complexity to mass transport effects in the phase-transfer system, which can hide the true kinetics of fluorination and any associated rate acceleration, as well as to the complex speciation of boronic acid (boroxine)/alcohol mixtures (see below).

(12) A 1:1 mixture of allylic alcohol and phenylboronic acid in toluene-d_8 reached an equilibrium composition after 2 h, giving a ratio of monoester to free alcohol of 0.76:1. Upon addition of 4Å MS, monoester as well as higher order condensation products were observed, giving an overall ratio of esterified to free alcohol of 3.3:1 (see the Supporting Information).

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(14) Subjection of the homoallylic alcohol corresponding to **1a** to the optimized conditions delivered the bishomoallylic fluoride in 48% yield as a racemic mixture (see the Supporting Information), illustrating the importance of placing the directing group at an appropriate distance from the alkene.

(15) A disubstituted *cis*-allylic alcohol proved unreactive, even at elevated temperatures (40−80 °C).

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