Highly Diastereoselective and General Synthesis of Primary β-Fluoroamines

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Abstract

(dr >20:1)   (dr >20:1)
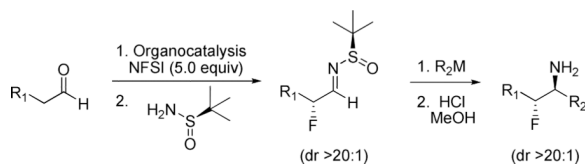
A short, high yielding protocol has been developed for the highly diastereoselective (dr >20:1) and general synthesis of primary β-fluoroamines by the enantioselective α-fluorination of aldehydes, conversion into the *N*-sulfinyl aldimine, nucleophilic addition of various organometallic species and 1° amine liberation.

β-Fluoroamines are common moieties in drug candidates as the β-fluorine atom can lower pK_a (diminish ancillary pharmacology), enhance binding interactions, improve metabolic stability and increase CNS penetration.[1–6] Despite their value, few methods exist for the general and stereoselective synthesis of primary β-fluoroamines outside of the classical DAST approaches which are plagued with rearranged and dehydrated products.[7–10] Alternate routes have emerged based on the diastereoselective reduction of α-fluoroimines, hydrofluorination of epoxides with further manipulation to provide β-fluoroamines, or tandem conjugate addition-fluorination sequences; however, all of these routes lack generality (inability to incorporate diversity) or display preference for either the *anti* or *syn* products.[11–14]

Recently, we reported a one-pot protocol to provide pharmaceutically relevant chiral β-fluoroamines via organocatalysis (Figure 1, eq 1).[15] In this Letter, we describe a novel methodology for the general synthesis of primary β-fluoroamines in high yield and diastereoselectivity employing organocatalytic α-fluorination of aldehydes,[16] Ellman *N*-sulfinyl aldimine technology,[17–21] nucleophilic addition of organometallic species[22–25] and 1° amine liberation (Figure 1, eq 2). This methodology affords complete control of the two contiguous stereogenic centers based on the chirality of the organocatalyst and sulfimine employed as well as on the transiton state (metal-chelate versus non-metal chelate transition states, MCTS and NMCTS, respectively) that the organometallic species adopts.

Key to the success of this approach is the ability to trap the incipient chiral α-fluoroaldehyde with the Ellman *tert*-butanesulfonamide to form the corresponding α-fluoro-*N*-sulfinylaldimine in high diastereomeric ratio (dr). A number of conditions were surveyed

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(time, dessicant, equivalents of NFSI) for the conversion of hydrocinnamaldehyde **1** to β-fluoro-*N*-sulfinylaldimine **4** (Scheme 1). Ultimately, we found that 5.0 equivalents of NFSI, 20 mol% (*R*)-**2**, Ti(OEt)$_4$ as dessicant with (R)-*tert*-butanesulfinamide **3** and a five hour reaction time was optimal to deliver **4** in >20:1 dr (as judged by ^{19}F NMR). Employing these conditions, a variety of diverse aldehydes could be converted into their corresponding β-fluoro-*N*-sulfinylaldimines **5**–**7** in good isolated yield (67–75%) for the two steps and with up to >20:1 d.r. (Figure 1). Here, substrates with handles for further elaboration were tolerated, such as the phthalimide congener **5**, a progenitor for basic amine analogues, the olefin in **6** for subsequent manipulations and a benzyl protected alcohol congener **7**.

With α-fluoro-*N*-sulfinylaldimine **4** in hand, we examined the additon of a number of organometallic nucleophiles to add unprecedented diversity to the primary β-fluoroamine scaffold and access derivatives previously unavailable. We first explored Grignard reagents (Scheme 2), and found a wide range of diverse R groups were tolerated affording the sulfinamide-protected primary β-fluoroamines **8a–c** in good isolated yields (72–92%) and >20:1 dr (as determined by ^{19}F NMR).[22] The *anti*-diastereomer of the β-fluoroamine formed predominantly as expected due to the known metal-chelated transition state (see inset under arrow) for **8a** and **8b**. The *syn*-diastereomer was formed in the case of **8c**, as a result of additional coordination to the acetal oxygen, in accordance with the work of Ellman.[23]

Due to the extensive diversity and availability of functionalized boronic acids, we next explored boronic acid additions. Under Batey's mild Rh(I) catalysis protocol,[24] a diverse group of aryl boronic acids (electron-rich, biaryl, and heterocyclic congeners), smoothly afforded the target adducts **9a–c** in 65–91% yield and once again in >20:1 dr (Scheme 3). In this instance, the *syn*-diastereomers of the β-fluoroamines are formed based on the known addition of the aryl rhodium species through a non-metal chelated transition state.[24]

Lin and co-workers previously demonstrated that indium-mediated allylations (In(0), allyl bromide in aqueous NaBr) of (*R*)-*N*-tert-butanesulfinylimines provides the (*S*)-adducts as confirmed by single X-ray crystallography.[25] To further add structural diversity to the primary β-fluoroamine scaffolds accessible through this approach, we employed Lin's protocol with our β-fluoro-*N*-sulfinylaldimine **4** (Scheme 4). As expected, *anti*-diastereomers of the sulfinamide-protected β-fluoroamine products **10** were produced in good yields (66–90%) and up to 9:1 dr. Here, we could install additional stereogenic centers (**10b**) and allene moieties (**10c**).

We also hoped to expand this protocol to include β-amino-alcohols. Following the work of Xu and Lin,[26] the SmI$_2$-induced reductive aldehyde cross-coupling with our β-fluoro-*N*-sulfinylaldimine **4** (Scheme 5) produced the target sulfinamide-protected primary β-fluoro-β'-amino-alcohols **11a–c** in excellent yields (80–87%) and once again with high dr (>20:1).

An attractive feature of the Ellman sulfinamide-protected primary amines is the generality and ease of deprotection.[17–26] Treatment of a representative example **8b** with HCl in dioxane at room temperature smoothly affords the desired primary β-fluoroamine congener **12** in greater than 90% yield and without loss of sterochemical integrity (Scheme 6). In our drug discovery efforts, we have deprotected numerous congeners of **8b**, and have never observed issues with stereochemical integrity or clean deprotections.

Finally, we wanted to apply this methodology to cyclic primary β-fluoroamines, as this pharmacophore has proven to be an important component of therapeutics, such as BACE inhibitors.[27,28] Classically, cyclic, racemic *trans*-primary β-fluoroamines (±)-**13** are prepared by the ring opening of aziridines with nucleophilic fluoride, followed by deprotection (Figure 2, eq 1).[8,27,28] Cyclic, racemic *cis*-primary β-fluoroamines (±)-**14** are prepared by fluorination of a silyl enol ether, followed by reductive amination and

deprotection (Figure 2, eq 1).[27,28] Overall, yields are modest to low (average 12% overall) for the racemic, cyclic primary β-fluoroamines and require several steps. In order to access enantiopure derivatives, heroic chiral chromatography is performed on either the free amine, or more likely, a protected form that introduces a chromophore, followed by chiral chromatography and deprotection. Ultimately, pure enantiomers of *trans*-**13** and *cis*-**14** are arrived at in typically less than 3% overall yield. In contrast, our methodology can provide rapid, high yielding access to either *cis*- or *trans*-cyclic primary β-fluoroamines with high enantioselectivity based on the chirality of the organocatalyst and the sulfinylamine employed. For example (Scheme 7), an indium-mediated allylation of **6** with allyl bromide gives **15** in 90% yield and 9:1 dr (if allyl Grignard employed, comparable yield, but >20:1 dr). Ring closing metathesis with Grubbs II affords cyclohexene **16** in 85% yield. Hydrogenation and standard acid-mediated deprotection provides chiral cyclic primary β-fluoroamine **18** in 70% overall yield for the four step sequence, a notable improvement over the classical route. The relative stereochemistry of **18** was confirmed by correlation with previously reported ^{19}F NMR shifts for *cis*- (−197 ppm) and *trans*-cyclic β-fluoroamines (−180 ppm), wherein **18** dsiplayed a singlet at −198 ppm.[29]

In summary, we have developed a highly diastereoselective and general synthesis of primary β-fluoroamines using a combination of organocatalysis and Ellman *N*-sulfinylaldimine technology to enable the preparation of all possible stereoisomers in high isolated yields. Importantly, this methodology provides access to primary β-fluoramine chemotypes that are generally not accessible, or difficult to prepare, through current chemistries, as well as providing a significant improvement for the synthesis of cyclic primary β-fluoroamines. Further refinements are in progess and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Chiral β-Fluoroamines via Organocatalysis
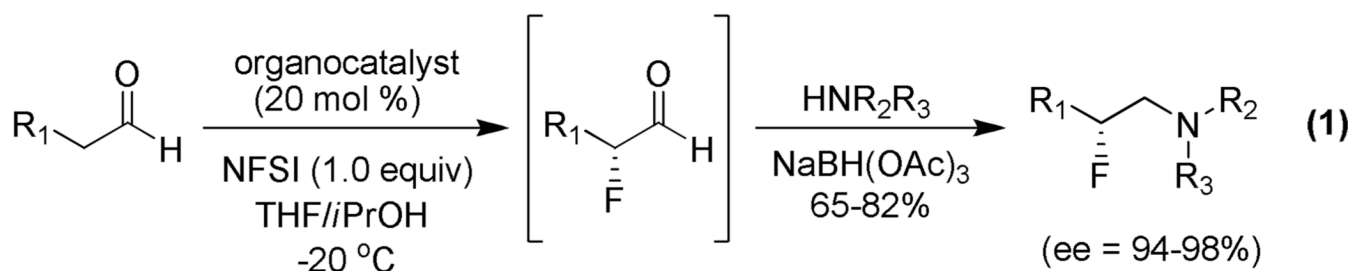
Highly Diastereoselective Synthesis of Primary β-Fluoroamines
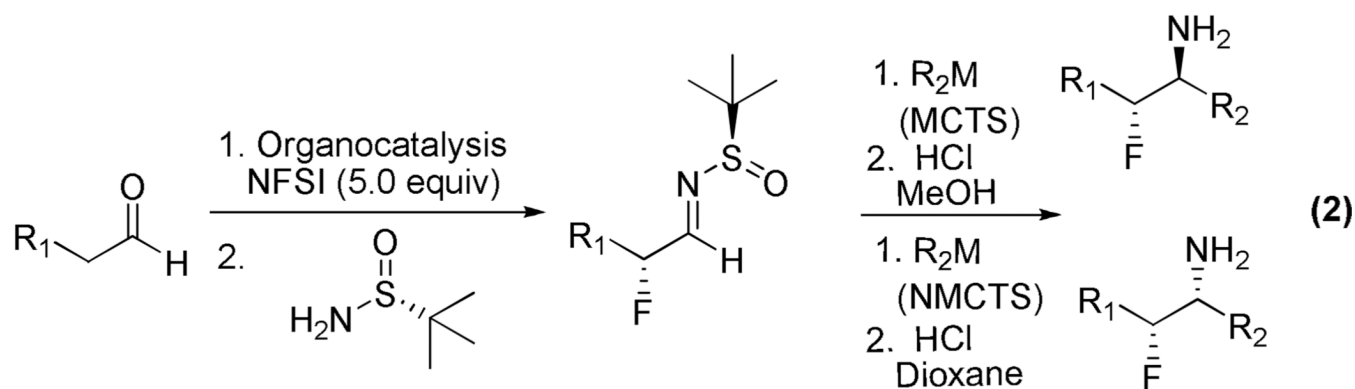
Figure 1.
Organocatalytic Approach to Chiral β-Fluoroamines and Envisioned Route to Chiral
Primary β-Fluoroamines.
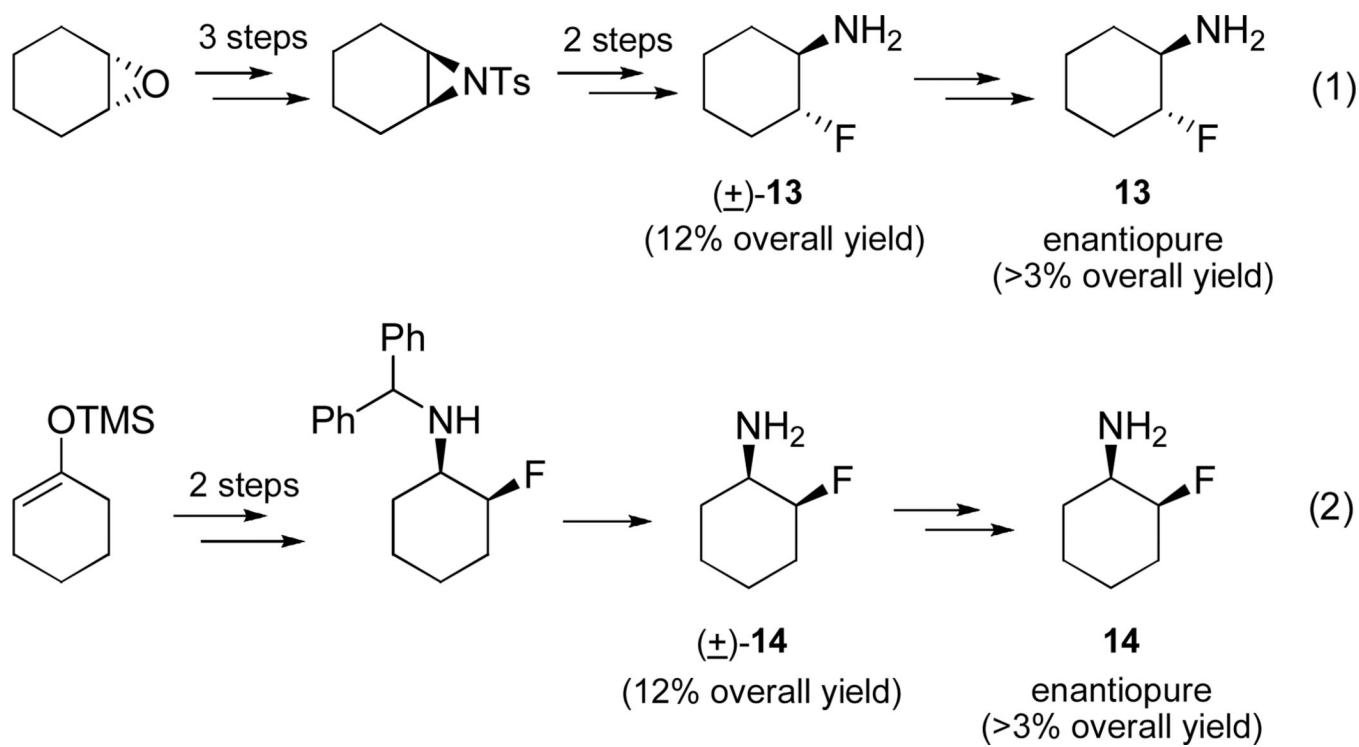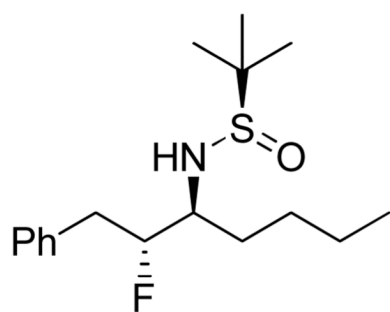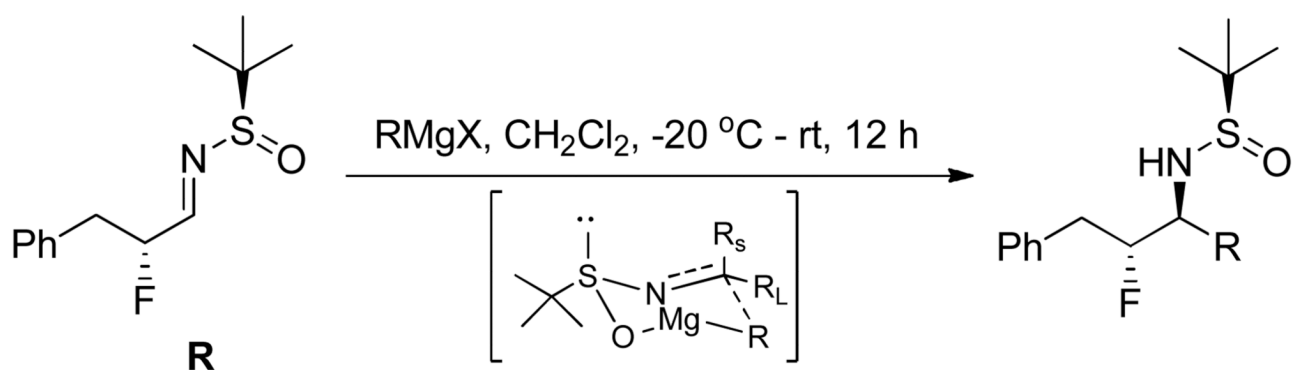
Figure 2.
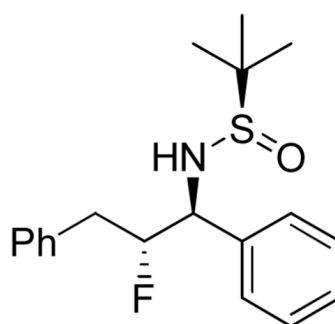Standard Synthetic Route to *trans*- and *cis*-Racemic and Enantiopure Cyclic Primary β-Fluoroamines.
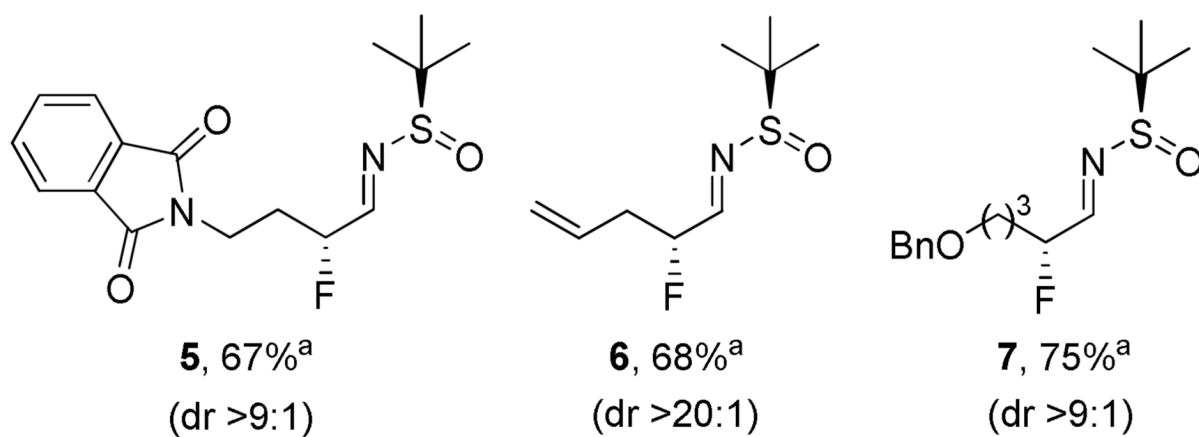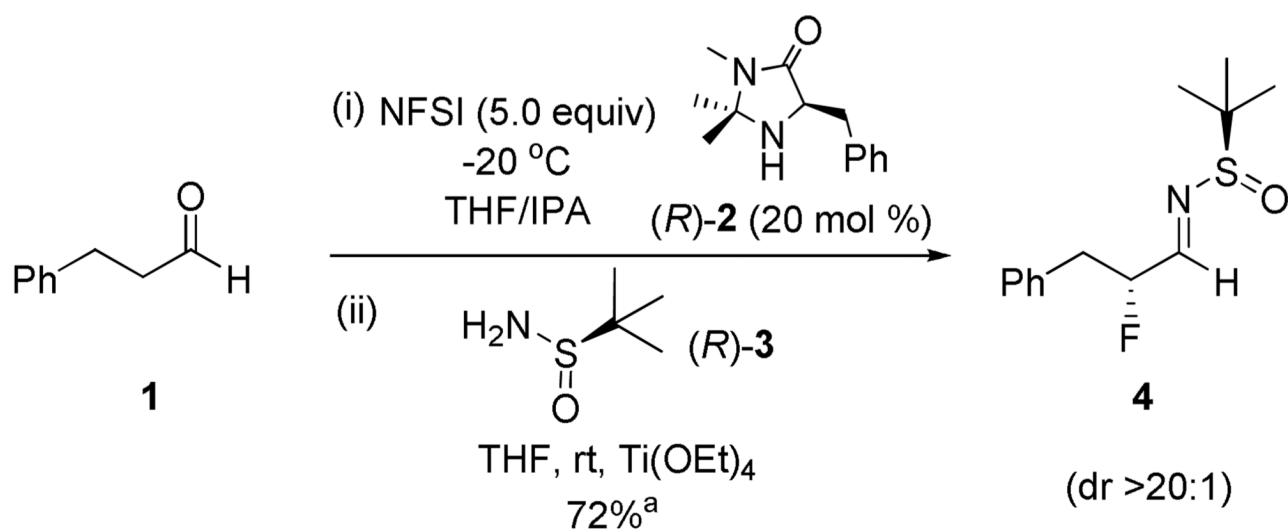
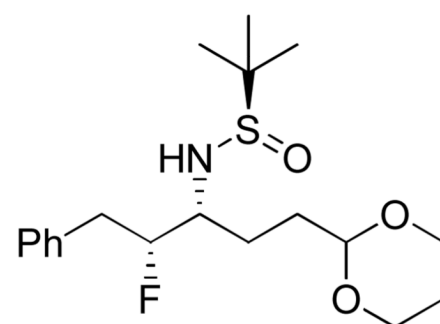^adiastereomeric ratio (dr) determined by ¹⁹F NMR.

Scheme 1.
Optimization of α-Fluoro-*N*-Sulfinyl Aldimine **4** Formation and Substrate Scope.

Scheme 2.
Scope of Grignard Additon to **4** to Deliver Sulfinamide-Protected Primary β-Fluoroamines **8a–c**.
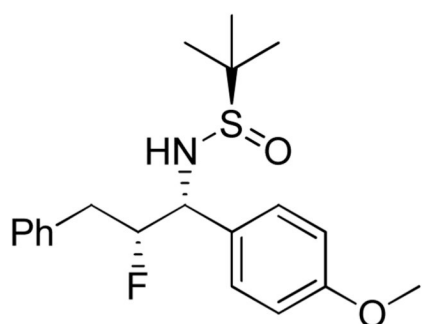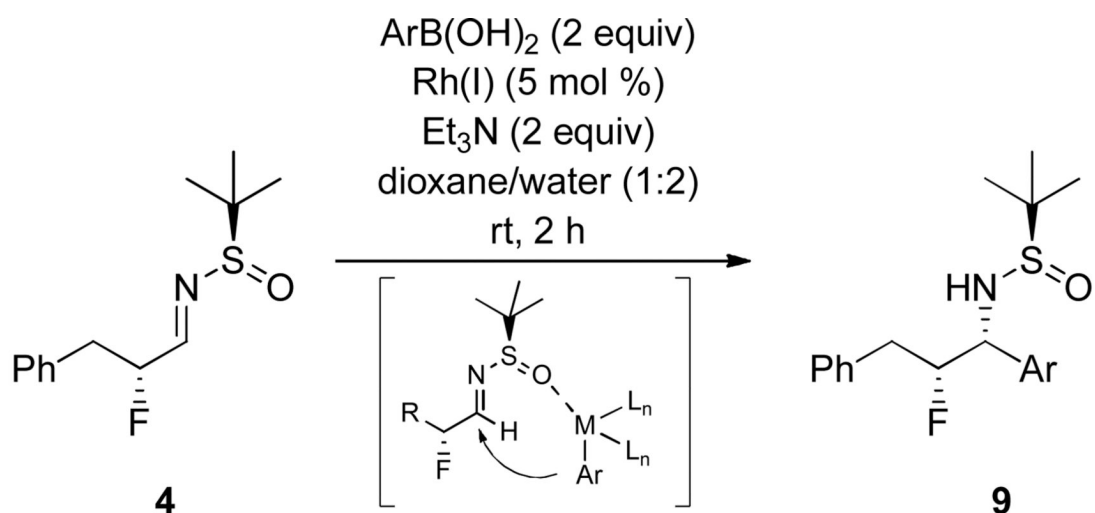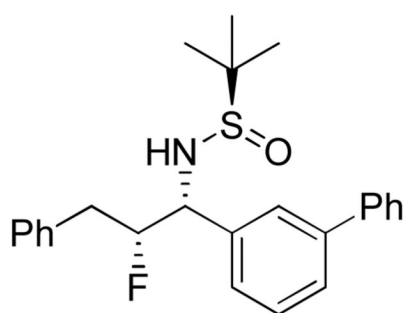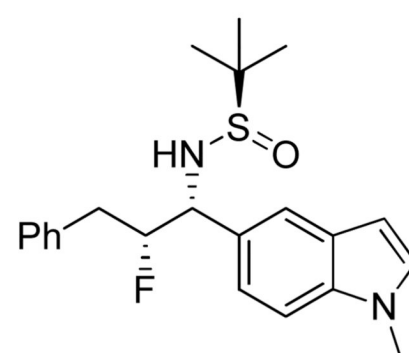
Scheme 3.
Scope of Boronic Acid Additon to **4** to Deliver Sulfinamide-Protected Primary β-Fluoroamines **9a–e**.

10a, 90%[a]
(dr = 9:1)

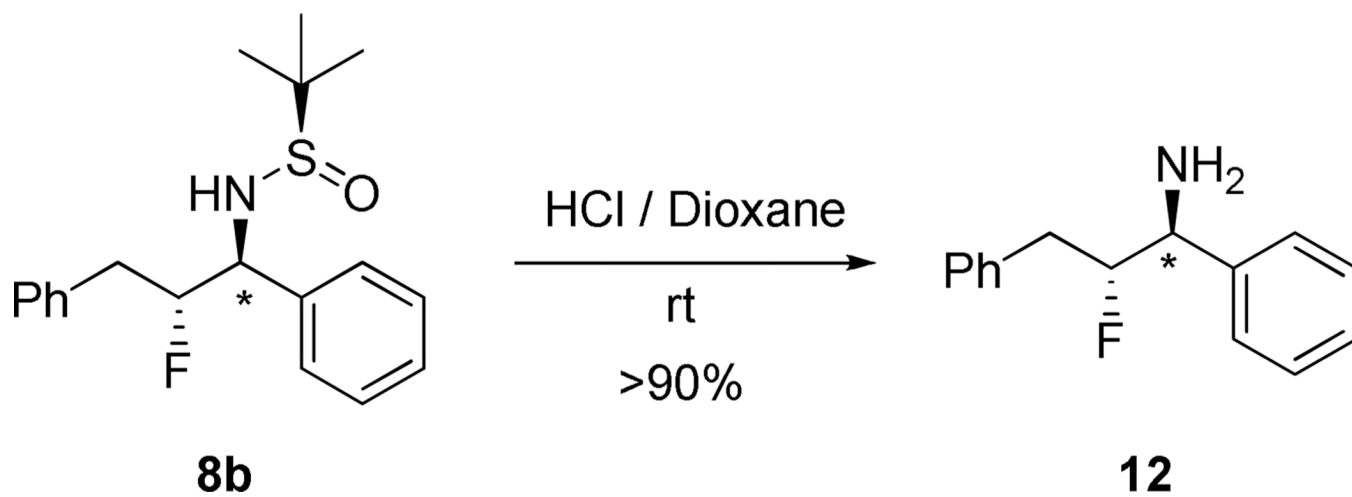**10b**, 82%[a]
(dr = 9:1)

10c, 78%[a]
(dr = 4:1)
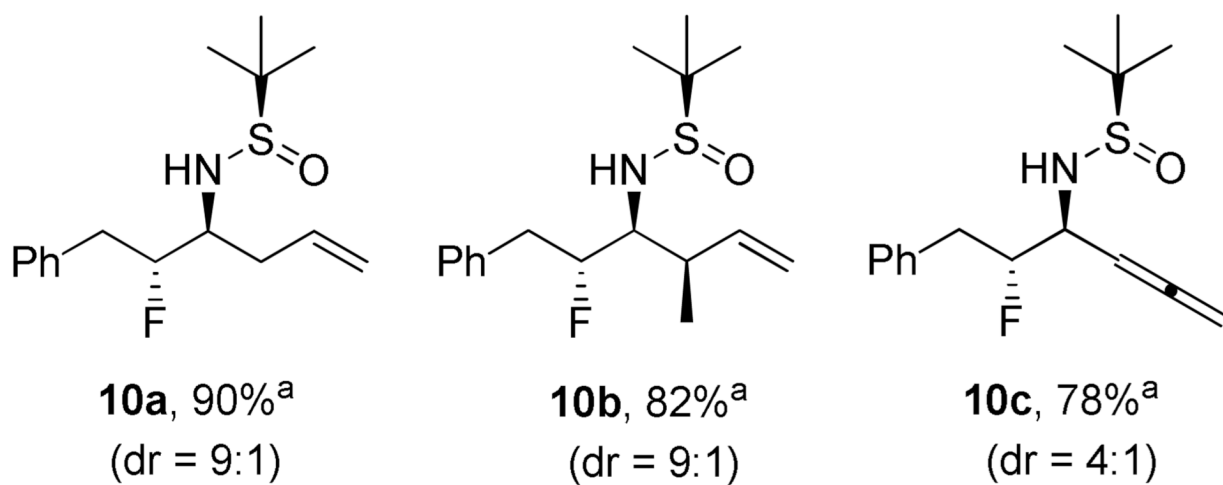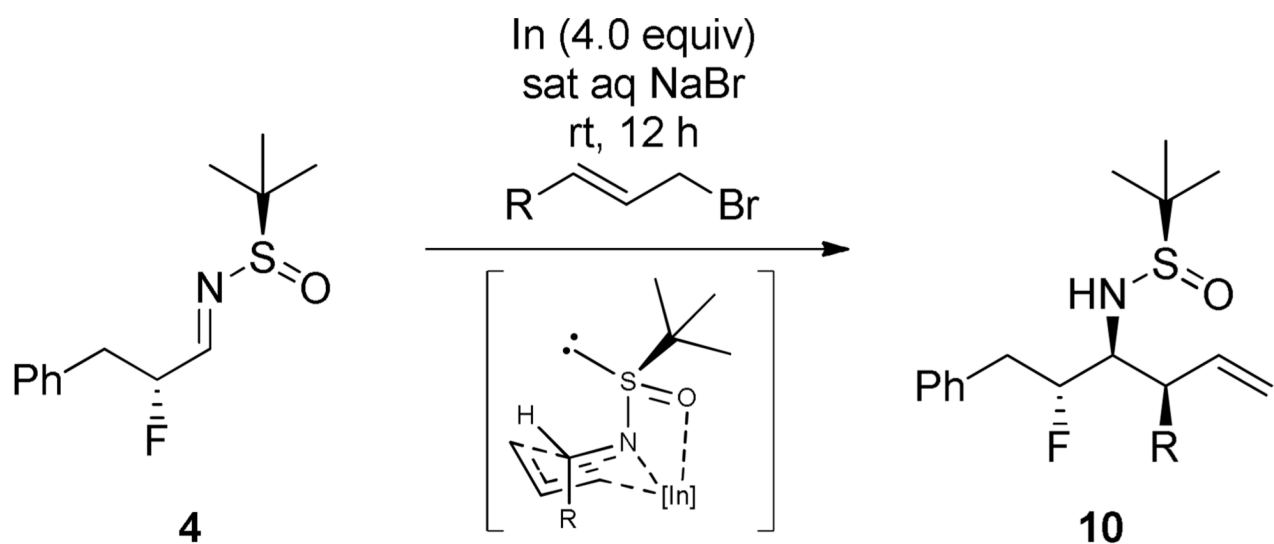
[a]With 0.5 mmol **4**.

Scheme 4.
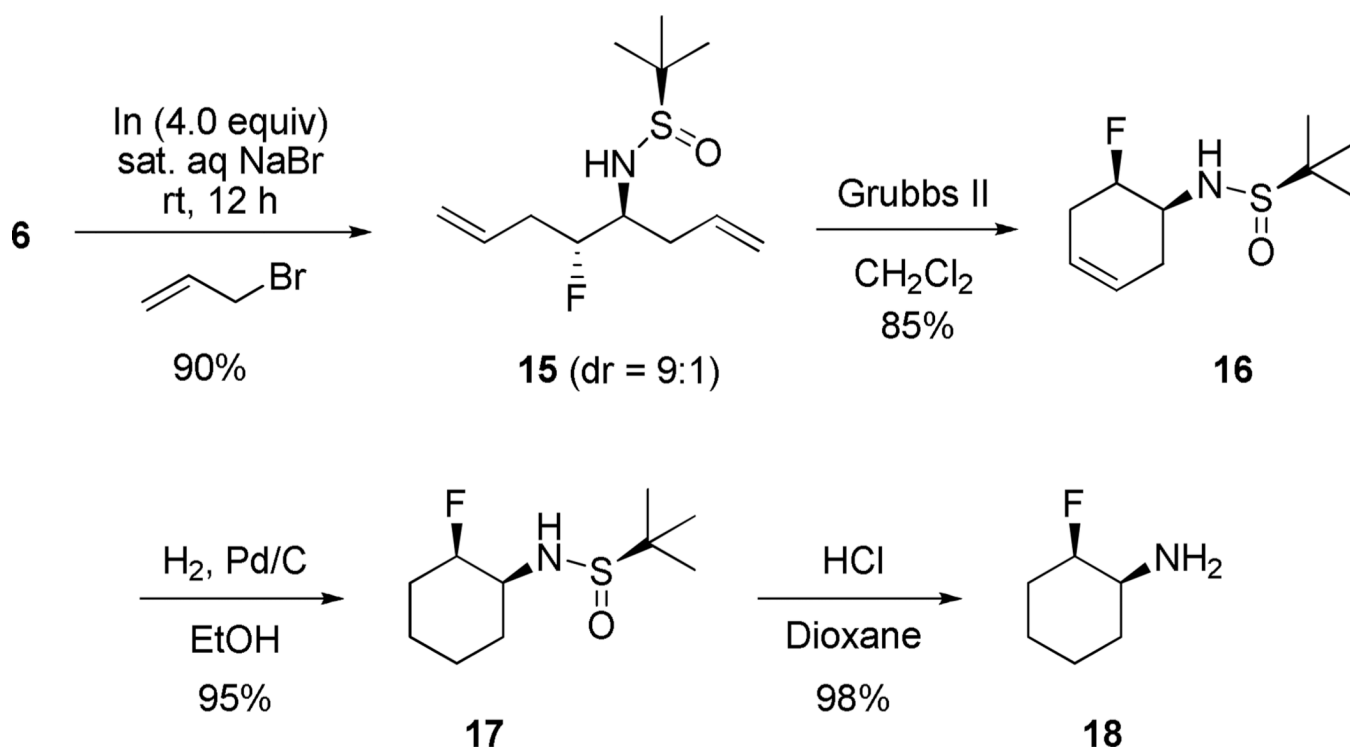Scope of In-Mediated Allylation of **4** to Deliver Sulfinamide-Protected Primary β-Fluoroamines **10a–c**.
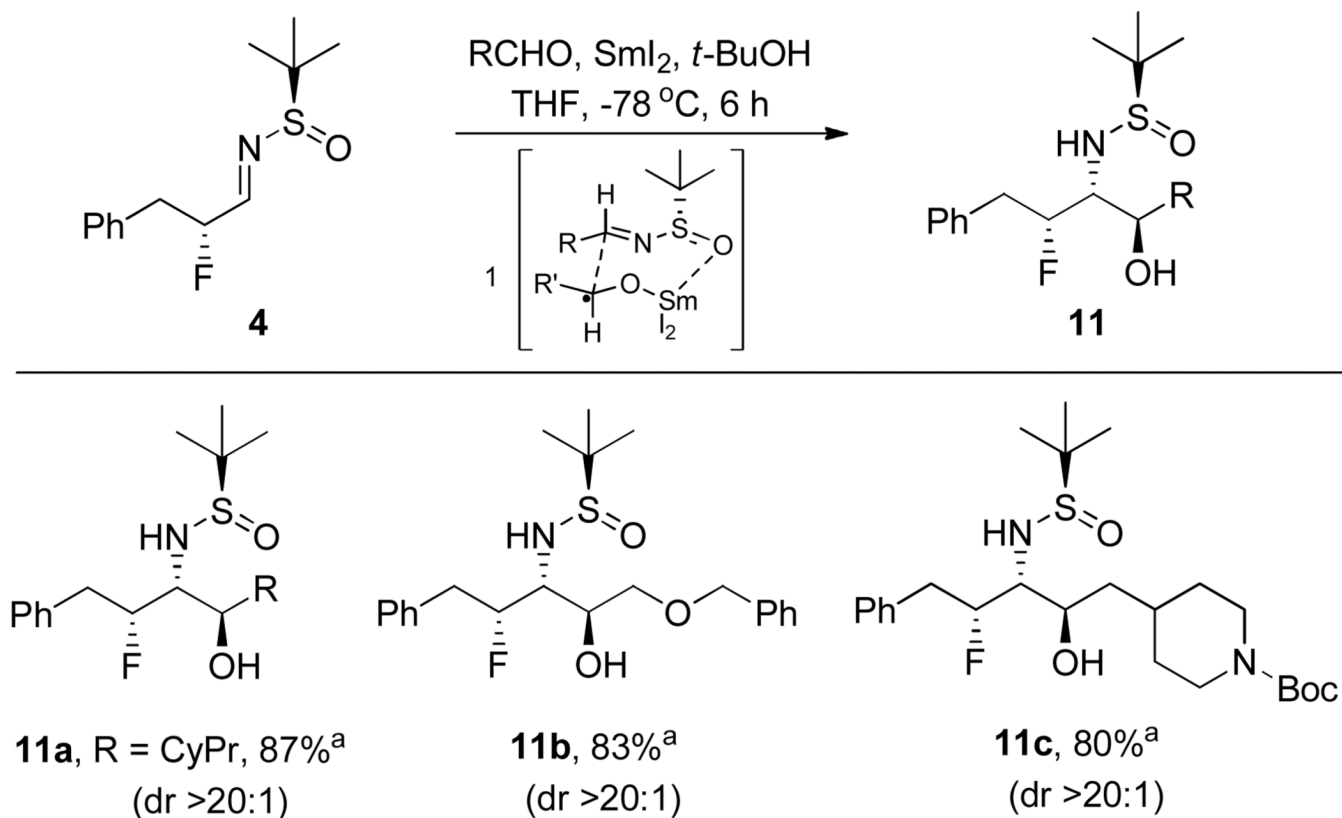
Scheme 5.
Scope of SmI$_2$-Induced Reductive Aldehyde Coupling of **4** to Deliver Sulfinamide-Protected Primary β-Fluoro-β'-Amino Alcohols **11a–c**.

Scheme 6.
Deprotection to Afford 1° β-Fluoroamine **12**

Scheme 7.
Access to Chiral, Cyclic 1° β-Fluoroamine **18**.