Fluorinated Amine Stereotriads via Allene Amination

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Abstract

The incorporation of fluorine into organic scaffolds often improves the bioactivity of pharmaceutically relevant compounds. C–F/C–N/C–O stereotriad motifs are prevalent in antivirals, neuraminidase inhibitors, and modulators of androgen receptors, but are challenging to install. An oxidative allene amination strategy using Selectfluor rapidly delivers triply functionalized triads of the form C–F/C–N/C–O, exhibiting good scope and diastereoselectivity for all *syn* products. The resulting stereotriads are readily transformed into fluorinated pyrrolidines and protected α-, β-, and γ-amino acids.

Graphical abstract
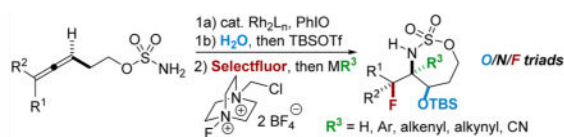
The introduction of fluorine into organic compounds is a popular strategy to improve the physical properties of molecules that range from pharmaceuticals and agrochemicals to advanced materials, polymers, and ligands.[1] Fluorine substitution often results in increased lipophilicity and bioavailability, promotes hydrophobic interactions between the drug and binding sites on receptors or enzymes, and imparts higher oxidative and thermal stability to a molecule as compared to the corresponding C–Hbonds.[2] The recent burst of activity directed toward the development of reagents and methods to introduce fluorine into organic scaffolds points to the continued need for approaches that furnish complex, highly functionalized heterotriad motifs, especially ones that are found in useful bioactive molecules (Figure 1).[3,4]

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Our group has previously developed oxidative amination strategies that install a new heteroatom at each of the sites of unsaturation in an allene substrate such as **1**, where a bicyclic methyleneaziridine **2** functions as the key intermediate (Scheme 1).[5] These allenes are easily synthesized from the corresponding propargyl alcohols through a three-step sequence involving a Johnson–Claisen rearrangement using $(EtO)_3CMe$, followed by $LiAlH_4$ reduction and sulfamate formation.[5a,d,f,i] Employing an enantioenriched propargyl alcohol in the allene synthesis delivers efficient axial-to-point chirality transfer to furnish enantioenriched stereotriads.[5a,i,j] However, our early efforts to incorporate valuable fluorines into the triad products **3** delivered only moderate yields and poor *dr*; stimulating further efforts to improve upon these initial results. In this letter, we report methods to introduce fluorine into allenes in both an electrophilic and nucleophilic manner to provide novel building blocks not easily synthesized using alkene functionalization strategies. In particular, oxidative allene amination methodologies are enabling for providing access to quaternary fluorine-bearing stereocenters difficult to prepare through deoxyfluorination protocols that are best-suited for the synthesis of primary and secondary alkyl fluorides.[6]

The first challenge was to identify the appropriate nucleophile/electrophile combinations capable of furnishing high *dr* in the oxidative allene amination to furnish the desired fluorinated stereotriads. A variety of nucleophiles are known to successfully open the intermediate bicyclic methyleneaziridine resulting from Rh-catalyzed aziridination of **4** (Scheme 1), including H_2O, MeOH, PhSH, and $PhNH_2$.[5a] Unfortunately, treatment of the corresponding enesulfamates with an array of electrophilic fluoride reagents, including Selectfluor, NFSI, 1-fluoropyridinium tetrafluoroborate, and 2,6-dichloro-1-fluoropyridinium tetrafluoroborate, showed variable *dr* or unproductive reaction in the imine formation. Eventually, we found that the combination of a bulky OTBS group at C1 of the enesulfamate **5** with Selectfluor enabled promising diastereocontrol in the addition of **5** (Table 1, entry 1) to the electrophile, furnishing **6a** as the major stereoisomer. $MeNO_2$ and MeCN proved to be the best solvents, but $MeNO_2$ showed minimal loss in yield and *dr* when the temperature was increased from 60 to 90 °C (Table 1, compare entries 2 vs 4–6), in contrast to the drop in yield noted when reactions in MeCN were run at higher temperatures (compare entry 1 vs 3). Increasing the equivalents of Selectfluor (entry 7) resulted in no improvement in the yield or the *dr*; therefore, the reaction conditions in entry 5 were chosen for further study.

The stereochemistry of the major imine product **6a** was confirmed to be 1,3-*syn* diastereomer by subsequent reduction to **7a**. The observed *syn* geometry is consistent with the model proposed in Figure 2, where the conformation **A** is less favored as compared to **B**, due to the $A^{1,3}$ strain generated by interactions between the sterically bulky OTBS group and the C_5H_{11} side chain that reside in the same plane. Relief of this $A^{1,3}$ strain drives the enesulfamate to adopt a conformation where the Selectfluor favors approach from the face opposite to the OTBS group, as illustrated in **B**. This rationale explains why the installation of small groups at C1 in our preliminary studies resulted in low and variable diastereoselectivities.

Reaction of **5** with Selectfluor, coupled with subsequent reduction of the imine stereoisomer **6a** with $Me_4NHB(OAc)_3$, could be carried out in one pot to furnish the 1,2-*syn*:2,3-*syn*

amine triad product **7a** as the major diastereomer (Table 2); two minor diastereomers were also observed (see the Supporting Information (SI) for details). Again, the minimization of $A^{1,3}$ strain in the imine **6a** likely drives the observed stereochemical outcome in the reduction, where the relative all-*syn* configuration of the three new sp³ stereogenic centers of **7a** was confirmed by single crystal X-ray crystallography (see the SI for details). Carbon nucleophiles, including Grignard reagents and Bu₄NCN, could be employed instead of a hydride source to furnish the stereotriads **8a**–**10a** in good yields and with *dr* of up to >20:1. The relative stereochemistry of **10a** was confirmed by X-ray crystallography (see the SI for details) to ensure that carbon nucleophiles behave similarly to hydrides. The very different dipole moments of the products **7a**–**10a** permitted ready separation of the diastereomers by column chromatography.

The scope of the reaction was explored using a series of 1,3-di- and 1,3,3-trisubstituted allenes (Table 3). Increasing the bulk of the C3 R group to an *ⁱ*Pr in **11** was not well-tolerated and gave **11a** in a low 19% yield and a 3:1 *dr* after reduction with Me₄N(OAc)₃BH. However, fluorination proceeded more smoothly when the allene side chains in **12**–**14** contained vinyl, phenyl, and silyl ether groups, giving moderate to good yields and *dr* of **12a**–**14a** after the reduction. Decreasing the size of the C3 substituent had no detrimental impact, as **15a** was obtained in 69% yield and 11:1 *dr*. Interestingly, even 1,3,3-trisubstituted allenes **16** and **17**, which previously failed to give either good yields or *dr* in oxidative allene aminations, were successful using this fluorination protocol. Reduction of the intermediate imines with Me₄N(OAc)₃BH delivered **16a** in 56% yield and >19:1 *dr* over the two steps. We were pleased to note that carbon nucleophiles, including HCCMgBr or Bu₄NCN, were also effective and resulted in the production of stereotriads **16b** and **16c**, containing two adjacent and fully substituted stereocenters in excellent *dr* of >19:1. Even when the sterics of the two alkyl groups on C3 of the original allene substrate were similar, as in the Et and Me groups of **17**, the triads **17a**–**c** could be obtained in diastereoselectivities ranging from 4:1 to >19:1, albeit in lowered yields. These densely functionalized motifs are not readily accessible from conventional olefin oxidation methodologies or aziridine ring-opening.

Additional substitutions in the allene tethers of **18**–**20** would be expected to influence the conformation of the intermediate enesulfamate, which, in turn, would be likely to impact the stereochemical outcome of the electrophilic fluorination. The diastereoselectivities in the fluorination of substrates **18**–**20** were 3:1, 3:1, and 6:3:2:1, respectively. The models in Figure 3 help to explain the observed stereochemical outcomes. For substrate **18**, there is a preference to avoid the eclipsed conformation in which OTBS and the methyl substituents are in close proximity. Thus, a gauche conformation is more favored, where the OTBS substituent is almost perpendicular to the ring. This results in effective blocking of the top face of the ring and increases the *dr* to 3:1. In terms of substrate **19**, a conformation where the OTBS and methyl substituents are *anti* to each other minimizes both $A^{1,3}$ strain between OTBS and the C₅H₁₁ side chain, as well as the gauche interaction between the OTBS and the adjacent methyl group. However, this conformation resulted in a *dr* of 3:1, due to the methyl group blocking the bottom face of the ring. In **20**, the ring is forced into a conformation that avoids the *syn*-pentane interaction between the isopropyl and the OTBS

groups. This orients the OTBS group a bit more in the plane of the ring; therefore, it is less effective at blocking the top face of the ring and the *dr* is lowered to 6:3:2:1.

The fluorinated amine triads proved to be useful and flexible building blocks for the synthesis of novel pyrrolidines and unnatural amino acid scaffolds (Scheme 2). For example, N-Boc protection and a NaI-mediated ring contraction of **7a** yielded the fluorinated pyrrolidine **28** in a good yield of 72% over the two steps and in a *dr* > 19:1. This motif appears in bioactive molecules that include the powerful glucosidase inhibitor 2,5-dideoxy-2,5-imino-D-mannitol (DMDP)[7] and various inhibitors of purine nucleoside phosphorylase (PNP).[8] Fluorinated amino acids are important building blocks in the design of hyperstable protein folds. They have also played roles in directing protein–protein interactions[9] and can act as potential antitumor agents or antimicrobial agents.[10] The use of fluorinated, unnatural amino acids in such applications could prove interesting and can be readily accessed in a few steps from either fluorinated triad **7a** or **9a**, as illustrated in the remainder of Scheme 2. For example, the ozonolysis of **9a** was followed by a standard Pinnick oxidation to afford the *α*-amino acid precursor **29** with no loss in the stereochemical information contained in the precursor. An alternative approach could employ the Strecker product **10a** (see Table 2), with hydrolysis of the nitrile delivering the same product **29**. N-Boc protection/ring-opening/elimination of **7a**, similar to that previously reported,[5j] furnished **30**. Compound **30** could be further elaborated into the protected *β*-amino acid **31** through a simple sequence of ozonolysis, Pinnick oxidation, and esterification. The same **30** was transformed into the protected *γ*-amino acid **32** by first carrying out a hydroboration reaction, followed by a RuCl$_3$-catalyzed oxidation of the alcohol to the carboxylic acid.

In conclusion, we have demonstrated that allenes can be converted into stereochemically complex and densely functionalized C–F/C–N/C–O stereotriad motifs in a two-pot process. Allene aziridination, ring-opening, and protection of the alcohol with a bulky TBS group furnish enesulfamates with high regiocontrol and *E:Z* selectivity, even when differentiating between groups as similar as Me and Et. Selectfluor was the most effective electrophilic fluorination reagent; reduction of the intermediate imine with either hydride or carbon-based nucleophiles furnished the products with reasonable scope and diastereoselectivity. Especially noteworthy was the ability to generate motifs with adjacent fluorine- and amine-bearing quaternary stereocenters in excellent *dr*. The C–F/C–N/C–O motifs can be readily transformed into fluorinated pyrrolidines and protected unnatural *α*-, *β*-, and *γ*-amino acids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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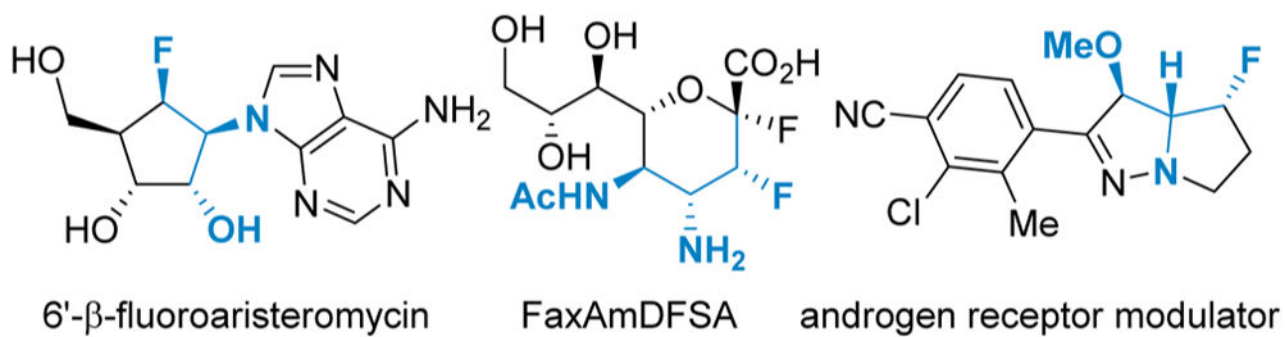
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Figure 1.
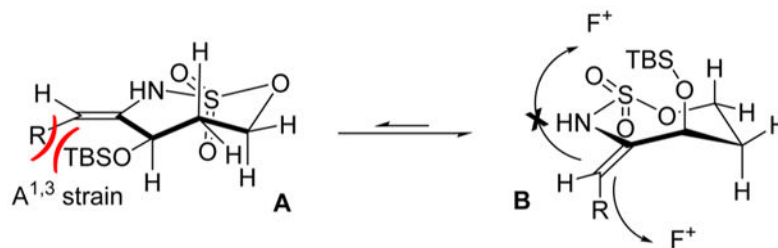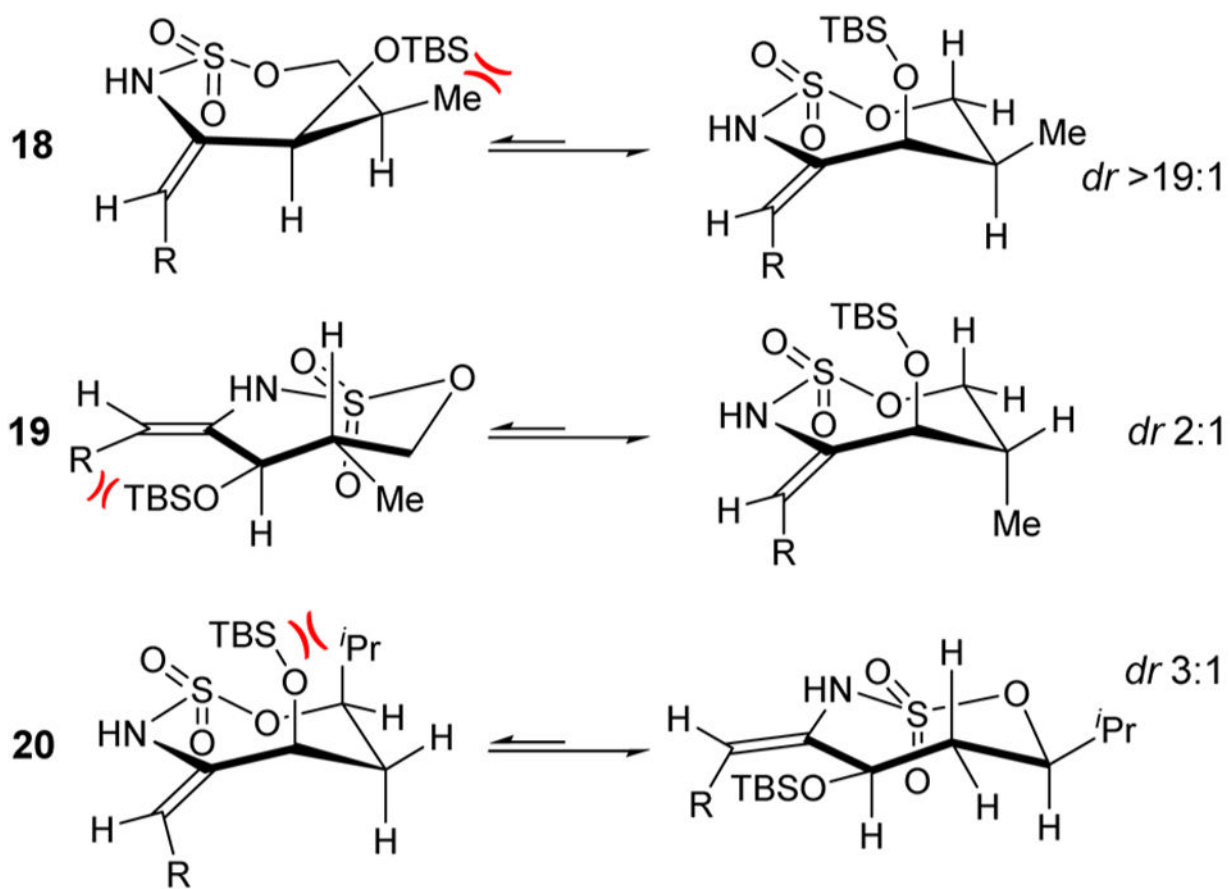Bioactive molecules containing fluorinated amine heterotriads.
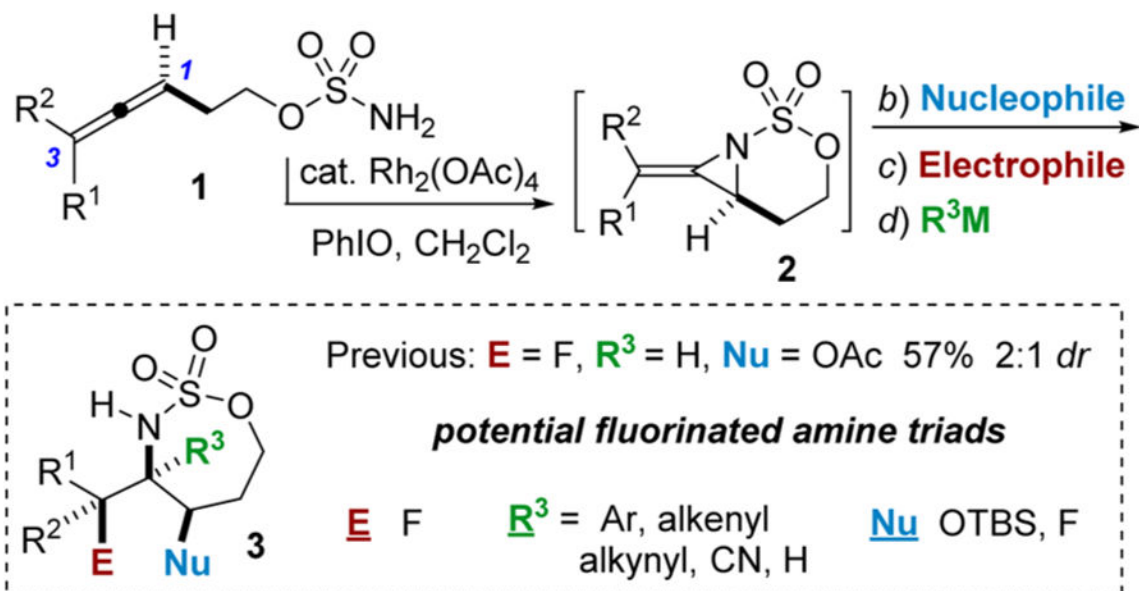
Figure 2.
Model rationalizing the observed overall *syn* selectivity in electrophilic fluorinations of enesulfamates.

Figure 3.
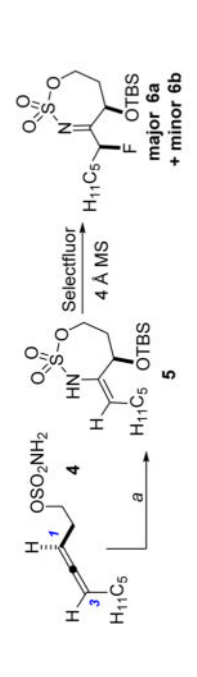Model rationalizing the observed *dr* in electrophilic fluorination of tethered enesulfamates.

Scheme 1.
Strategy for Generating Fluorinated Amine 'Triads'

28

>19:1 *dr*

72%

1) 1.5 equiv Et$_3$N
1.5 equiv Boc$_2$O
10 mol % DMAP
CH$_2$Cl$_2$, rt, 40 min

2) 1.8 equiv NaI then
6.6 equiv NaH
DMF, 68 °C, 10.5 h

7a

R = H; **7a**

ref 5j

81%

R = CH=CH$_2$; **9a**

1) O$_3$, CH$_2$Cl$_2$, -78 °C then
2 equiv Et$_3$N, rt, 3.5 h, 84%

2) NaClO$_2$/NaH$_2$PO$_4$/H$_2$O$_2$
CH$_3$CN, 46%

29

a) O$_3$, CH$_2$Cl$_2$, -78 °C
then 2 equiv Et$_3$N, rt, 1 h

b) NaClO$_2$, NaH$_2$PO$_4$,
30% aq. H$_2$O$_2$, MeCN,
0 °C to rt, 12 h

c) TMSCHN$_2$, MeOH, 0 °C.

57% over 3 steps

30

d) 0.83 equiv BH$_3$, THF,
0 °C, 24 h, then 4.2
equiv NaOH, 8.2 equiv
30% aq. H$_2$O$_2$, 30 min

e) 10 mol% RuCl$_3$•H$_2$O,
4.5 equiv NaIO$_4$, MeCN/
H$_2$O/CCl$_4$, 0 °C, 27 h

45% over 2 steps

31

β–amino acid

32

γ–amino acid

Scheme 2.
Motifs Available from Fluorinated Triads

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Table 1

Optimization of the Electrophilic Fluorination Reaction in the Reaction of 5 with Selectfluor
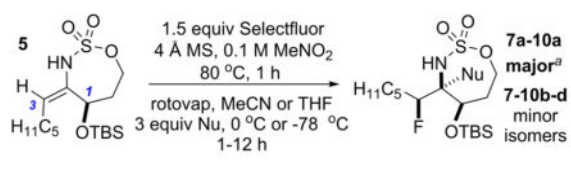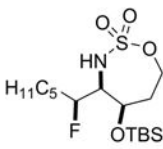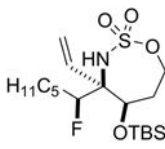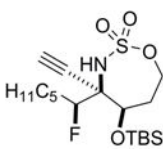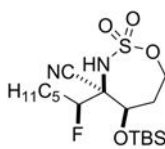
entry	solvent	F+ (equiv)	temp (°C)	time (h)	yield[b]	dr (6a:6b)[b]
1	CD$_3$CN	1.5	60	4	69%	8.6:1
2	CD$_3$NO$_2$	1.5	60	4	77%	8.7:1
3	CD$_3$CN	1.5	80	2	56%	7.9:1
4	CD$_3$NO$_2$	1.5	80	2	72%	8:1
5	CD$_3$NO$_2$	1.5	80	1	76%	8.3:1
6	CD$_3$NO$_2$	1.5	90	0.5	77%	7.7:1
7	CD$_3$NO$_2$	2.5	80	1	75%	8.4:1

[a] 0.75 mol % Rh$_2$(OAc)$_4$, PhIO, CH$_2$Cl$_2$, rt; H$_2$O; then 4 Å MS, TBSOTf, Et$_3$N.

[b] Yields and dr (syn:anti) determined by ^{1}H and ^{19}F NMR using 1-Br-2,5-difluorobenzene as the internal standard.

Table 2

Scope of Nucleophiles in the Fluorination of 5

product	yield dr	product	yield dr
7a	66%[b] 7.3:1.4:1	9a	61%[d] 18:3:1
8a	70%[c] 8:1	10a	41%[e] >20:1

[a] Yield of the isolated major diastereomer. After the fluorination and filtration were complete, the following reagents were added.

[b] 0.1 M MeCN/AcOH, 3 equiv of $Me_4N(OAc)_3BH$, 0 °C to rt, 12 h.
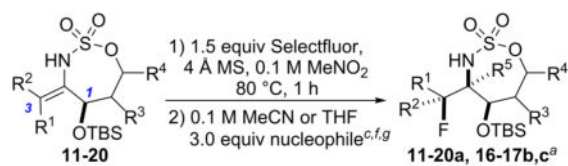
[c] 0.1 M THF, 3 equiv of HCCMgBr, 0 °C, 1 h.

[d] 0.1 M THF, 3 equiv of CH_2=CHMgBr, −78 °C, 30 min.

[e] 0.1 M MeCN, 2.0 equiv of Bu_4NCN, rt, 2.6 h.

Table 3

Scope of 1,2-*syn*:2,3-*syn* Fluorinated Amine Triads

product	yield dr	product	yield dr
	19% **11a** (*dr* 3:1)[b,c]		68% **12a** (*dr* 9:1)[c,d]
	58% **13a** (*dr* 8:1)[b,c]		69% **14a** (*dr* 7:1.5:1)[c,d]
	69% **15a** (*dr* 11:1)[c,d]		56% **16a** (*dr* >19:1)[c,d]
	52% **16b** (*dr* >19:1)[d,e]		89% **16c** (*dr* >19:1)[d,e,g]
	27% **17a** (*dr* >19:1)[d,e]		28% **17b** (*dr* 4:1)[d,f]
	75% **17c** (*dr* 5:1)[d,e,g]		51% **18a** (*dr* 3:1)[c,d]

product	yield dr	product	yield dr
	24% **19a** (*dr* 3:1)[c,d]		41% **20a** (*dr* 6:3:2:1)[c,d]

[a]Listed yields are for the isolated major diastereomer.

[b]Diastereomer ratios of the crude product are in parentheses.

[c]0.1 M MeCN/AcOH, 3 equiv of Me_4N $(OAc)_3BH$, 0 °C to rt, 12 h.

[d]Isolated *dr*.

[e]Fluorination in MeCN, 40 0 °C, 14 h.

[f]0.1 M THF, 3 equiv of HCCMgBr, 0 °C, 1 h.

[g]0.1 M MeCN, 2.0 equiv of Bu_4NCN, rt, 2.6 h.