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Organocatalytic Enantioselective Olefin Aminofluorination

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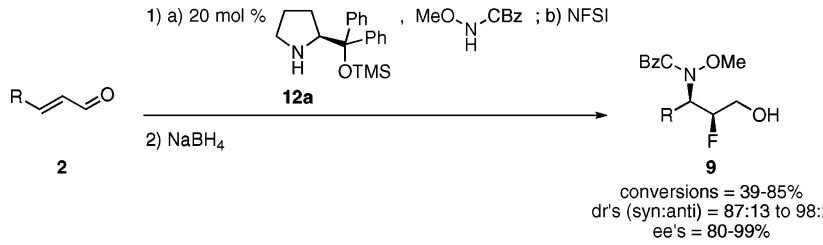
ABSTRACT



Chiral *β*-fluoroamines are increasingly prevalent in medicinal compounds, but there are few efficient methods to access them from achiral starting materials. To address this, a multicomponent organocascade reaction was developed in which chiral α-fluoro-*β*-amino aldehydes were generated *in a single flask* from achiral α,*β*-unsaturated aldehydes (2), using catalyst 12a. Conversions up to 85%, dr's up to 98:2 and ee's up to 99% of the corresponding alcohol (9) were achieved in this reaction.

The incorporation of fluorine into medicinal compounds is increasingly prevalent with "20−25% of drugs in the pharmaceutical pipeline contain[ing] at least one fluorine atom."[1] MK-0731 (**1**, Figure 1) is one example, developed by Merck for the treatment of Taxane-refractory cancer.[2] More specifically, *β*-fluoroamines, as in **1**, are increasingly common substructures in medicinal compounds, because fluorine can improve the bioavailability of amine drugs by decreasing the basicity of neighboring amine groups.[1] Additionally, α-fluoro-*β*-amino acids are useful building blocks of therapeutic *β*-peptides.[3] Despite the increasing use of *β*-fluoroamino moieties in medicinal compounds, efficient synthetic methods for their preparation are sparse. Recently,

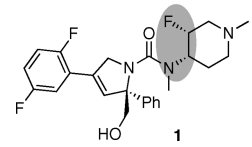


Figure 1. MK-0731.

Pd-catalyzed olefin aminofluorination reactions were reported, in which *achiral* *β*-fluoroamines were generated in a single step.[4] *β*-Fluoroamines containing a single stereocenter can be produced using a one-pot organocatalytic α-fluorination/reductive amination protocol.[5] Accessing chiral *β*-fluoroamines with *vicinal* stereocenters (as in **1**) usually requires the use of chiral starting materials. We are aware of only two efficient (i.e., one-pot) methods for preparing these compounds from achiral starting materials. One is an asymmetric olefin aminofluorination reaction, in which chiral *β*-fluoroamines are generated from achiral α,*β*-unsaturated esters.[6] The asymmetric induction in this method is not catalytic; stoichiometric quantitites of a chiral amine nucleophile are used. In addition, an organocatalytic Mannich reaction using α-fluoro-*β*-dicarbonyl compounds as nucleophiles produced chiral *β*-fluoroamines in high yield and

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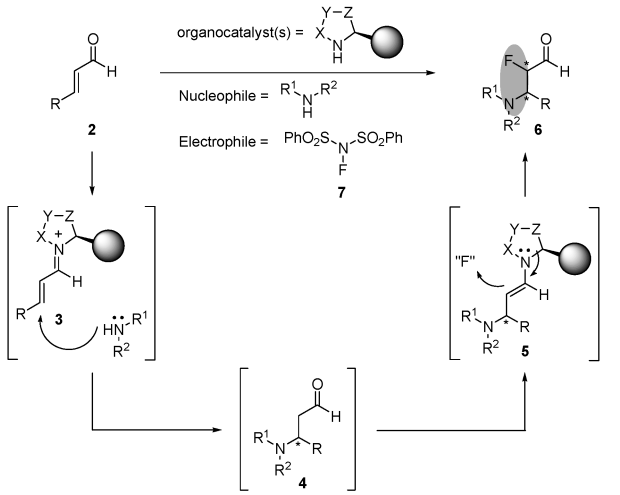
selectivity (dr ≥92:8).[7] However, the dr decreased to 4:1 during subsequent decarboxylation to produce α-fluoro-β-amino acid derivatives.[7b] We supposed that an organocascade reaction (Scheme 1) would be a highly selective and green chemical method for accessing β-fluoroamines, including α-fluoro-β-amino acid derivatives, containing vicinal stereocenters.

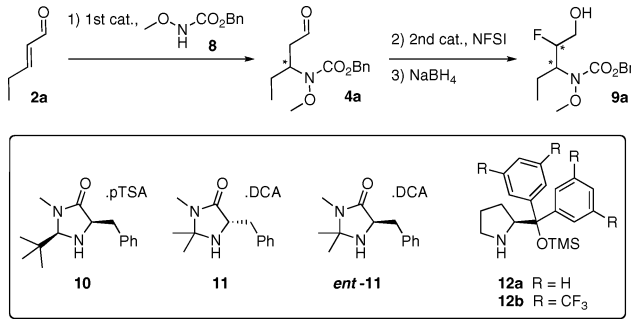
Scheme 1. Proposed One-Pot Organocascade Reaction



Iminium-catalyzed conjugate additions of amine nucleophiles to α,β-unsaturated aldehydes have been reported,[8] as have enamine-catalyzed fluorinations of saturated aldehydes.[9] It was anticipated that these two complementary functionalizations could be combined as an organocatalytic asymmetric olefin aminofluorination reaction. As such, an achiral α,β-unsaturated aldehyde (**2**) and an iminium catalyst would combine to form chiral iminium **3**. Iminium **3** would undergo an asymmetric conjugate addition of an amine nucleophile, liberating saturated aldehyde **4**. In the presence of an enamine catalyst, chiral enamine **5** would be generated. Reaction of enamine **5** with an electrophilic source of fluorine would produce chiral β-fluoroamine **6**.

The development of a one-pot organocatalytic asymmetric olefin aminofluorination reaction began using amine nucleophile **8** and *N*-fluorosulfonimide (NFSI, **7**) as an electrophilic source of fluorine (Table 1). It was anticipated that it would be necessary to use an iminium organocatalyst in conjunction with an enamine catalyst,[10] as no single organocatalyst had been reported for both fluorination reactions and aza-Michael additions of amines of type **8**. Investigations began with iminium catalyst **10**, the most selective MacMillan catalyst for the conjugate addition of amine nucleophiles of type **8** to α,β-unsaturated aldehydes.[8a] Using optimal solvent and temperature conditions reported for this reaction, the CBZ-protected amine (**8**) produced **4a** in higher yield and ee than the corresponding BOC protected amine (entries 1 and 2). Compound **4a** was subsequently fluorinated using catalyst **11** (or ***ent*-11**), the most selective MacMillan catalyst for fluorinations.[9b] Under a variety of solvent and temperature conditions, **9a** was produced as, at most, a 1:3 (*syn*:*anti*) ratio of diastereomers (entry 3). We simultaneously discovered that **10** *nonselectively* catalyzed the

Table 1. Reaction Development[a,b]



	step 1					step 2					
entry	1st cat.	solvent	*t* (°C)	yield **4a**(%)	ee **4a**(%)[c]	2nd cat.	solvent	*t* (°C)	convn **9a** (%)[d]	dr **9a** (*syn*:*anti*)[c]	ee **9a** (%)[c]
1[e]	**10**	$CHCl_3$	−20	70	80 (*S*)						
2	**10**	$CHCl_3$	−20	80	84 (*S*)						
3						**11**	$CHCl_3$/IPA (9:1)	−10	29	1:3	nd
4	**12a**	$CHCl_3$	−20	63	94 (*R*)						
5	**12a**	$CHCl_3$	−20			***ent*-11**	$CHCl_3$/IPA (9:1)	−10	nd	1:1	nd
6	**12a**	$CHCl_3$	−20			**11**	$CHCl_3$/IPA (9:1)	−10	46	1:3	nd
7	**12a**	$CHCl_3$	−20			**11**	$CHCl_3$/IPA (9:1)	rt	56	3:1	nd
8	**12a**	MTBE	rt				MTBE	0	59[f]	95:5	99

[a] Reaction conditions for step 1: **2a** (0.125 mmol), **8** (0.15 mmol), 1st cat. (0.025 mmol), solvent (0.5 mL), temp. [b] Reaction conditions for steps 2 and 3: (2) NFSI (0.125 mmol), 2nd cat. (0.025 mmol), solvent (0.5 mL), cosolvent (0.055 mL), temp; (3) $NaBH_4$ (0.25 mmol), MeOH (1 mL), 0 °C. [c] Determined by chiral phase HPLC. [d] Determined by ^1H NMR. [e] BOC-protected amine used. [f] Isolated yield.

fluorination step (data not shown). This would preclude the development of the organocatalytic olefin aminofluorination reaction as a highly selective one-pot process, as the presence of **10** during the fluorination step would erode the already modest selectivity attained using **11**.

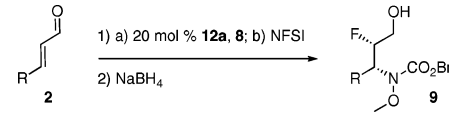
Investigations began anew using **12a**, the only other organocatalyst reported for the conjugate addition of amine nucleophiles of type **8** to α,β-unsaturated aldehydes.[8b] Pleasingly, this catalyst afforded **4a** in the highest ee obtained thus far (entry 4). Although **12a** can also participate in enamine catalysis, it was expected that this catalyst would not interfere in the subsequent fluorination step. Related catalyst **12b** was the only organocatalyst, aside from **11**, reported for highly selective fluorination reactions of saturated aldehydes.[9a] Jørgensen and co-workers ran **12b**-catalyzed fluorination reactions in methyl *tert*-butyl ether (MTBE), as they noted that **12b** was desilylated and thereby deactivated by NFSI in more polar solvents such as CH_2Cl_2.[9a] It was anticipated that catalyst **12a**, being more nucleophilic than **12b**, would be more rapidly deactivated by NFSI in polar solvents and would therefore not interfere with **11**-catalyzed fluorinations in 9:1 $CHCl_3$/*i*PrOH. When reactions were set up as one-pot procedures to test this, **9a** was once again produced as, at most, a 1:3 (*syn*:*anti*) ratio of diastereomers (entries 5 and 6).

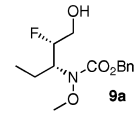
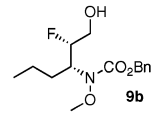
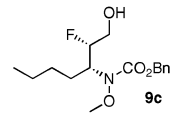
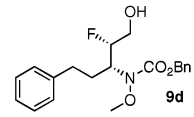
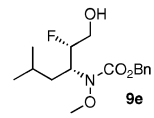
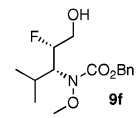
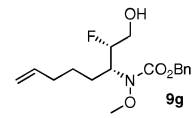
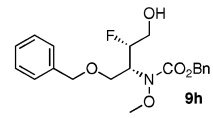
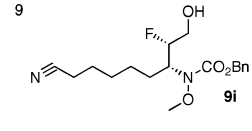
When the fluorination step was run at a higher temperature, the selectivity of the cascade process was reversed, and **9a** was generated as a 3:1 (*syn*:*anti*) ratio of diastereomers (entry 7). Evidently, and much to our surprise, the *syn* selectivity of catalyst **12a** was overriding the *anti* selectivity of catalyst **11** at higher temperatures. We then speculated that the olefin aminofluorination reaction could be catalyzed solely by **12a**, using MTBE as solvent to maximize the efficacy of **12a** in the fluorination step. Aldehyde **2a**, amine **8** and catalyst **12a** were combined in MTBE at rt. After 24 h, the reaction was cooled to 0 °C and NFSI was added. After workup and subsequent reduction, chiral β-fluoroamine **9a** was isolated in 59% yield, in 99% ee, and as a 95:5 (*syn*:*anti*) ratio of diastereomers (entry 8).

This is, in fact, the highest dr achieved in **12**-catalyzed organocascade reactions in which multiple carbon−heteroatom bonds are formed; dr's in a **12a**-catalyzed aminosulfenylation reaction ranged from 1:1 to 3:1 and those in a **12b**-catalyzed diamination reaction were 3:1 and 4:1.[8c,11] Furthermore, this is the first demonstration of the use of catalyst **12a** in a fluorination reaction.

Extensive optimization[12] revealed that modifying the reaction time and concentration was most effective for increasing the yield of **9a**, which was improved to 73% (average yield per step = 90%; Table 2, entry 1). Other α,β-

Table 2. Substrate Study[a]



entry	product	convn (%)[b,c]	dr (*syn*:*anti*)[d]	ee (%)[d]
1	 **9a**	85 (73)	95:5	99
2	 **9b**	72 (64)	94:6	99
3	 **9c**	76 (66)	95:5	99
4	 **9d**	61 (51)	95:5	98
5	 **9e**	63 (41)	90:10	99
6	 **9f**	39 (24)	98:2	80
7	 **9g**	79 (61)	93:7	99
8	 **9h**	71 (57)	87:13	99
9	 **9i**	57 (41)	91:9	99

[a] Reaction conditions: (1) (a) **2** (0.125 mmol), **8** (0.15 mmol), **12a** (0.025 mmol), MTBE (0.625 M), rt, 24−48 h; (b) NFSI (0.125 mmol), MTBE (0.25M), 0 °C, 40−72 h. (2) $NaBH_4$ (0.25 mmol), MeOH (1 mL), 0 °C. [b] Determined by ^1H NMR. [c] Numbers in parentheses are isolated yields. [d] Determined by chiral phase HPLC.

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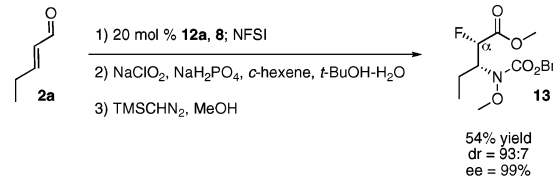
unsaturated aldehydes with linear alkyl substituents were effective in this reaction (entries 2 and 3). Branched alkyl substituents resulted in slightly reduced conversions but maintained the high selectivity of this process (entries 4 and 5). Even α,β-unsaturated aldehydes with very bulky alkyl substituents underwent this transformation, albeit in low conversion and reduced ee (entry 6). Importantly, the presence of other olefins, ether protecting groups, and remote reactive functional groups, such as cyano groups, is tolerated (entries 7−9). A cinnamaldehyde derivative was unreactive under the reaction conditions.

Notably, crude aldehyde products can be converted into chiral α-fluoro-β-amino acid derivatives with virtually *no loss of selectivity* (Scheme 2). Conversion of **4e** to a known compound and comparison of its optical rotation to the literature value established the stereochemistry of **4e** (and of the corresponding stereocenter in **9** and **13**) as *R*.[12] The relative stereochemistry of **13** (and by analogy **9**) was assigned as *threo* on the basis of the chemical shift of its α proton relative to that of the minor diastereomer.[12]

In conclusion, an organocatalytic asymmetric olefin aminofluorination reaction has been developed. This reaction generates chiral α-fluoro-β-amino aldehydes *in a single flask* from achiral α,β-unsaturated aldehydes in up to 85% conversion, 99% ee and 98:2 dr. Significantly, this methodology enables the rapid access of chiral α-fluoro-β-amino acids in outstanding dr and ee, from simple achiral starting materials. Further investigations into this organocascade reaction, including its synthetic applications, are presently underway.

Scheme 2. α-Fluoro-β-amino Acid Derivative



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Supporting Information Available: General experimental conditions and full characterization data for compounds **2i**, **9a**−**9i**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See Supporting Information