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A Highly Regio- and Stereoselective Synthesis of α-Fluorinated Imides via Fluorination of Chiral Enamides

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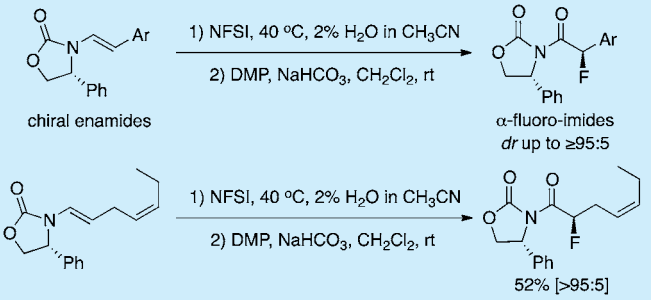
Supporting Information

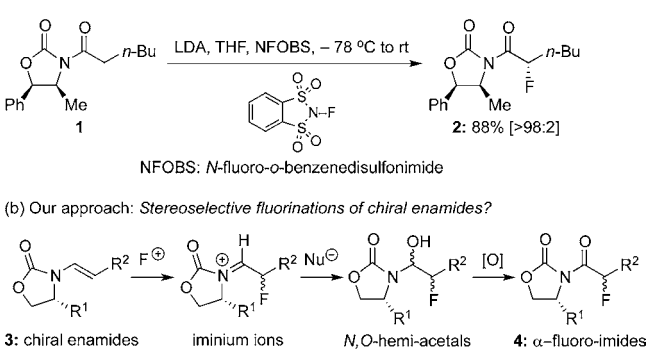
ABSTRACT: A highly π-facial selective and regioselective fluorination of chiral enamides is described. The reaction involves an enantioselective fluorination exclusively at the electron-rich enamide olefin with N−F reagents such as Selectfluor and *N*-fluoro-benzenesulfonimide [NFSI] accompanied by trapping of the β-fluoro-iminium cationic intermediate with water. The resulting *N,O*-hemiacetal could be oxidized using Dess-Martin periodinane, leading to an asymmetric sequence for syntheses of chiral α-fluoro-imides and optically enriched α-fluoro-ketones.



The importance of organo-fluorine compounds has been abundantly validated through a broad range of applications in medicinal chemistry and drug development[1] as well as material[2] and agrochemical sciences.[3] The incorporation of fluorine and/or fluorine-containing groups into an organic compound has often provided agents and materials with unique chemical, physical, and biological properties.[4] One of the major synthetic challenges in fluoro-organic chemistry is to asymmetrically construct fluorinated stereogenic carbon centers. Differding[5] demonstrated the first stoichiometric asymmetric fluorination of β-ketoester enolates with a chiral N−F (*N*-fluoroamine) reagent in 1988. Given the number of impressive examples of enantioselective fluorinations being reported over the past decade,[6] asymmetric fluorinations represent an area of immense interest from the synthetic community. In relevance to our work, Davis[7] reported an elegant synthesis of α-fluoro-imides using enolate derived from chiral imide **1** substituted with chiral oxazolidinone auxiliary[8] (**1** → **2** in Scheme 1). Our longstanding interest in the chemistry of enamides has drawn us to develop stereoselective fluorination methods using chiral enamides,[9] which has remained elusive. Such an approach in combination with an oxidative process (**3** → **4**) would represent a complementary approach to Davis' asymmetric approach to α-fluoro-imides.

With the nitrogen atom being substituted with an electron-withdrawing functionality, chiral enamides possess superior stability to their enamine counterparts, while maintaining excellent reactivities. This is evident by their recent emergence as another powerful chiral building block in organic synthesis.[10,11] In particular, chiral enamides have been employed in highly regio- and/or stereoselective Diels−Alder cycloadditions,[12] [2 + 2] cycloadditions,[13] cyclopropanation,[14] epoxidation,[15] and halo-etherification.[16] We wish to report here a highly regio- and stereoselective fluorination of chiral enamides for the synthesis of chiral α-fluoro-imides and optically enriched α-fluoro-ketones.

Scheme 1. Stereoselective Synthesis of α-Fluoro-imides



Our efforts commenced with exploring the right fluorination conditions using chiral enamide **3a** as the testing enamide, and with Selectflur,[17] *N*-fluoropyridinium triflate [Py-F],[18] and *N*-fluoro-benzenesulfonimide [NFSI][19] as the fluorinating agent. When reactions were carried out in CH_3CN at 40 °C, we found that it was faster with Selectflur (entry 1 in Table 1) and much slower with Py-F (entry 2), and that NFSI was the best N−F reagent[20] in terms of diastereoselectivity, leading to α-fluoro-imides **4a** and **4a′** as an isomeric mixture in 57% yield after DMP oxidation (entry 3).[21] We note here that attempts to directly

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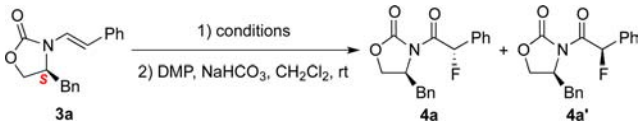
Table 1. Optimization of the Fluorination Conditions[a]



entry	solvent	reagent[a]	time [h]	yield [%][b] [dr][c]
1	CH_3CN	Selectfluor	0.5	29 [57:43]
2	CH_3CN	Py-F	24	26 [61:39]
3	CH_3CN	NFSI	9.5	57 [89:11]
4	anhyd CH_3CN[d]	NFSI	8	<10 [85:15]
5	2.0 equiv H_2O in CH_3CN	NFSI	8	43 [89:11]
6	1% H_2O in CH_3CN	NFSI	12	62 [91:9]
7	**2% H_2O in CH_3CN**	**NFSI**	**12**	**68 [91:9]**
8	5% H_2O in CH_3CN	NFSI	31	29 [91:9]
9[e]	2% H_2O in CH_3CN	NFSI	6	22 [71:29]

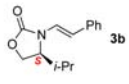
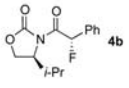
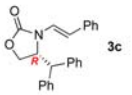
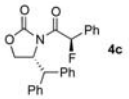
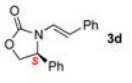
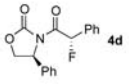
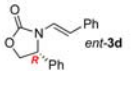
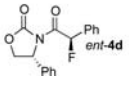
[a]In all reactions, 1.1 equiv of N−F reagent was added. Unless otherwise noted, reactions were run at 40 °C. DMP: Dess-Marin Periodinane; NSFI: *N*-fluoro-benzenesulfonimide; Py-F: *N*-fluoro-pyridinium triflate. [b]Yields were determined by ^{1}H NMR analysis using mesitylene as the internal standard. [c]Diastereomeric ratios [*dr*] were determined using ^{1}H or/and ^{19}F NMR spectroscopy. [d]CH_3CN distilled over CaH_2. [e]The reaction temperature is 80 °C.

work up the crude fluorination mixture without any oxidation protocols failed to give us the desired *N,O*-hemiacetal products, or the corresponding α-fluoro-aldehydes via hydrolysis.

Most notably, H_2O plays a significant role in this reaction. The use of anhydrous CH_3CN did afforded comparable diastereoselectivity, but the yield is very low (entry 4). The addition of 2.0 equiv, 1%, 2%, and 5% H_2O in the CH_3CN appeared to improve the efficiency (entries 5−8) with 2% H_2O being the most optimal (entry 7). On the other hand, when we increased the temperature from 40 to 80 °C, neither the *dr* ratio nor the yield was satisfactory.

To improve the diastereoselectivity, we examined a range of chiral auxiliaries as shown in Table 2. Enamide **3b** with the *i*-Pr-substituted Evans chiral auxiliary[22] gave α-fluoro-imide **4b** in 58% yield with a 93:7 *dr* ratio. Fluorination of chiral enamide **3c** substituted with the Sibi auxiliary[23] afforded **4c** in 51% yield (entry 2). When using the Ph-substituted Evans auxiliary,

Table 2. Effect of the Chiral Auxiliary on Selectivity[a]

entry	enamides	products	time [h]	yield [%][b][dr][c]
1	 3b	 4b	14	58 [93:7]
2	 3c	 4c	12	51 [91:9]
3	 3d	 4d	12	72 [>95:5]
4	 ent-3d	 ent-4d	12	63 [>95:5]

[a]Reaction condition: 1.1 equiv of NFSI, 2% H_2O in CH_3CN, 40 °C; and then, DMP, $NaHCO_3$, CH_2Cl_2, rt. [b]Isolated yields. [c]Diastereomeric ratios [*dr*] were determined by ^{1}H or/and ^{19}F NMR spectroscopy.

fluorinations of **3d** and *ent*-**3d** with NFSI at 40 °C in 2% H_2O in CH_3CN led to **4d** and *ent*-**4d**, respectively, in good yields and essentially as a single diastereomer (entries 3 and 4). X-ray structures of α-fluoro-imide **4b** and *ent*-**4d** allowed for unambiguous assignment of both stereochemical and structural integrity (Figure 1).

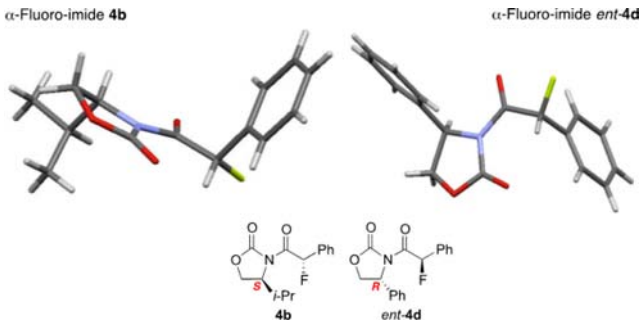
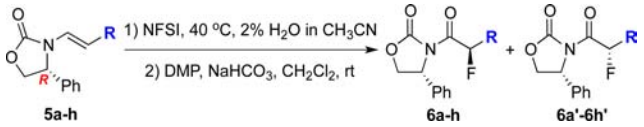


Figure 1. X-ray structures of α-fluoro-imides **4b** and *ent*-**4d**.

Success in finding chiral amides that can provide a high level of diastereoselectivity allowed us to broaden the scope of this fluorination significantly as shown in Table 3. For all examples in

Table 3. Stereoselective Fluorination of Chiral Enamides



entry	α-fluoro-imides: R =	time [h]	yield [%][a] [*dr*][b]
1	4-MeC_6H_4 (**6a**)	10	67 [94:6]
2	4-$MeOC_6H_4$ (**6b**)	12	42 [92:8]
3	4-$NO_2C_6H_4$ (**6c**)	140	71 [>95:5]
4	4-FC_6H_4 (**6d**)	12	61 [>95:5]
5	4-ClC_6H_4 (**6e**)	12	65 [>95:5]
6	4-BrC_6H_4 (**6f**)	14	69 [95:5]
7	2-ClC_6H_4 (**6g**)	12	59 [>95:5]
8	*n*-Pent (**6h**)	11	53 [>95:5]

[a]Isolated yields. [b]The diastereomeric ratio [*dr*] was determined by ^{1}H or/and ^{19}F NMR spectroscopy.

which a variety of different R substituents were evaluated, excellent diastereoselectivities of >92:8 and moderate-to-good yields were obtained. It is noteworthy that while electron-donating and -withdrawing substitution groups at the aryl does not influence diastereoselectivity, with a strong electron-withdrawing group, reactions indeed took a much longer time (see entry 3). Lastly, although predictable, these asymmetric fluorinations can indeed be highly regioselective in favor of the electron-rich enamide-olefin as demonstrated with fluorinations of chiral enamides **7** and **9** (Scheme 2).

While synthetically this method represents a stereoselective approach for constructing chiral α-fluoro-imides, mechanistically, this fluorination provides some insight into the chemistry of chiral enamides. On the basis of the observed stereochemical outcome, a proposed mechanistic model is shown in Scheme 3. We had calculated that the most stable conformation of these chiral enamides has the chiral oxazolidinone ring essentially coplanar with the alkene to maximize the delocalization of the nitrogen lone pair into the olefin.[24] With this conformational preference, the chiral oxazolidinone auxiliary plays a distinct role

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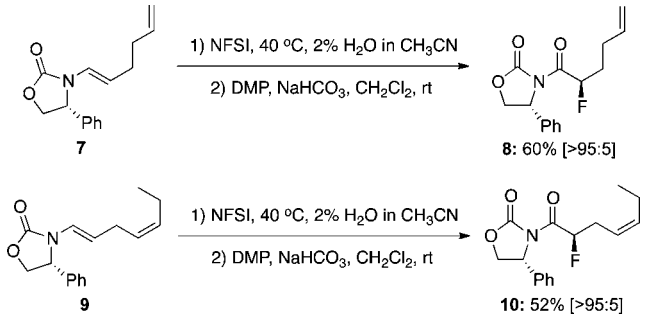
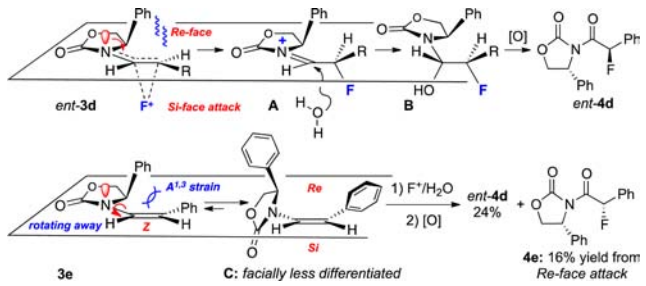
Scheme 2. A Regioselective Fluorination



Scheme 3. A Proposed Stereochemical Model

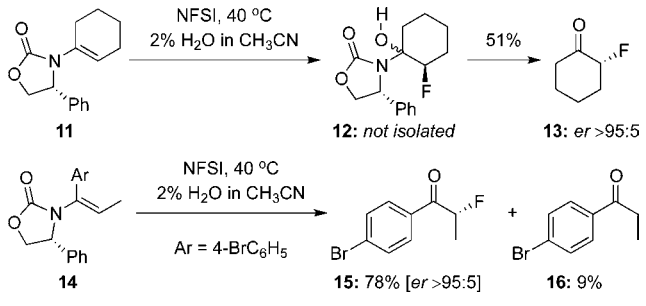


in providing a key facial bias for the fluorine to approach from the *Si*-face as represented in *ent*-**3d**. Subsequent trapping of the *N*-acyl iminium ion **A** with water can in principle be stereoselective, but this stereochemical information is lost in the ensuing oxidation.

On the other hand, for *Z*-enamides such as **3e**, the predicted selectivity would be poor based on this conformational model. To alleviate the allylic strain shown in **3e**, the chiral oxazolidinone ring needs to rotate away and can no longer be coplanar with the alkene, thereby leading much less differentiated π-faces [see **C**]. To support this model, we prepared *Z*-enamide **3e** and found that not only is the yield of its fluorination inferior to those of *E*-enamides but also the diastereoselectivity is diminished significantly.

Lastly, as a useful synthetic application, we examined asymmetric fluorinations of trisubstituted enamides. As shown in Scheme 4, optically enriched 2-fluorocyclohexanone **13**[25]

Scheme 4. Fluorinations of Trisubstituted Enamides



could be obtained directly from trisubstituted enamide **11** after a simple workup with the fluorinated *N*,*O*-hemiacetal intermediate **12** being insufficiently stable for isolation. Likewise, the use of enamide **14** led to α-fluorinated aryl ketone **15** in 78% yield with an *er* of ≥95:5. This is in direct contrast with our earlier attempts to isolate α-fluoro-aldehydes via hydrolysis of the corresponding *N*,*O*-hemiacetal intermediate from fluorinations of disubstituted enamides.

We have reported an asymmetric synthesis of α-fluoro-imides via fluorinations of chiral enamides. The reaction involves selectively fluorinating the electron-rich enamide olefin using Selectfluor and *N*-fluoro-benzenesulfonimide [NFSI] followed by trapping of a β-fluoro-iminium cationic intermediate with water and oxidation of the resulting *N*,*O*-hemiacetal. From a practical perspective, the reaction is operationally simple, requires inexpensive reagents and mild conditions, and provides chiral α-fluoro-imides and optically enriched α-fluoro-ketones in good yields and high selectivities.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures as well as NMR spectra, characterizations, and X-ray structural files (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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(25) The absolute stereochemistry of 2-fluorocyclohexanone **13** was confirmed through comparison of its optical rotation ($[\alpha]_D^{23}$ = +45.7 [*c* 0.73, $CHCl_3$]) with reported values (a) $[\alpha]_D^{23}$ = +54.8 [*c* 1.0, C_6H_6]: Enders, D.; Faure, S.; Potthoff, M.; Runsink, J. *Synthesis* **2001**, 2307. (b) $[\alpha]_D^{23}$ = +49.6 [*c* 0.9, C_6H_6]: Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 1738. For ketone **15**, it is assigned based on a mechanistic analogy with only the racemic form having been reported and the fact that the assignment of **13** is in good agreement with our stereochemical assessment for all other α-fluorinated-imides.

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