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Enantioselective Synthesis of α-Fluorinated β-Amino Acid Derivatives by an Asymmetric Mannich Reaction and Selective Deacylation/Decarboxylation Reactions

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Powerful probes for revealing the workings of biological systems can be prepared through the judicious replacement of hydrogen atoms with fluorine.[1] The C–F bond has a significant effect on the reactivity, stability, and bioavailability of molecules.[2] Thus, there is a strong demand for a wider availability of versatile fluorine-containing building blocks; enantiopure ones are particularly in demand.[3] The fluorinated amino acids[4] (F-AAs) impart unique properties when they were used in the modification of peptides and proteins in protein engineering. They are also ideal intermediates for drug-discovery programs and have found their way into drugs like Vaniqa (antineoplastic agent).[1] Fluorinated α-amino acids[5] (F-α-AAs) are also well known as irreversible inhibitors of pyridoxal phosphate-dependent enzymes. Conversely, much less is known about fluorinated β-amino acids (F-β-AAs).[5b,6]

As they are potential precursors for β-lactams, various strategies for the stereoselective synthesis of β-AAs have been reported.[6,7] Among these, the most robust and powerful method is attributed to the asymmetric Mannich reaction, of which several organocatalytic versions have been developed over the past few years.[8,9] However, the synthesis of F-β-AAs by using asymmetric Mannich reactions is still rare despite these developments. Furthermore, the synthetic route to α-fluorinated β-amino acids (α-F-β-AAs), particularly those containing chiral quaternary α-carbon center, is virtually unexplored.[10]

Recently, we reported the bicyclic, guanidine-catalyzed[11] formation of asymmetric C–F bonds using α-fluoro-β-ketoesters as fluorocarbon nucleophiles in highly enantio- and diastereoselective conjugate-addition and Mannich reactions.[11d] Such α-fluoro-β-ketoesters have also recently been exploited by the groups of Lu,[12] Maruoka,[13] and others.[14] Catalytic enantioselective nucleophilic fluorination is not common, and the other successful example is the use of 1-fluorobis(phenylsulfonyl)methane (FBSM). Shibata, Toru, and co-workers have reported the use of this fluorocarbon nucleophile in palladium-catalyzed, allylic-replacement,[15a] Mannich-type,[15b] and Michael reactions with α,β-unsaturated ketones.[15c] This fluoronucleophile was also used by Prakash, Olah, and co-workers in Mitsunobu[16a] and Michael addition to chalcones.[16b]

In our preliminary studies, we obtained excellent yield from the Mannich reaction between α-fluoro-β-ketoester **1a** and *N*-ethoxycarbonyl imine **2a**, although the enantio- and diastereoselectivities were moderate (Table 1, entry 1). Our experiences with bicyclic, guanidine-catalyzed, asymmetric reactions allowed us to predict that the catalyst system would respond well to changes in the steric properties of the substrates. Hence, we changed the *N*-ethoxycarbonyl imine **2a** to *N*-*tert*-butyloxycarbonyl (Boc) imine **2b**. The diastereoselectivity increased slightly, but the enantiomeric excess (*ee*) value decreased (Table 1, entry 2). We then worked on the α-fluoro-β-ketoester, and replaced the ester moiety with oxazolidinone, as it has an additional opportunity for hydrogen bonding due to the additional carbonyl groups. The lower reactivity of β-keto acetyloxazolidinone **1b** meant that the reaction with *N*-Boc imine **2b** had to be carried out at room temperature; a moderate *ee* value was obtained, but the diastereoselectivity was lost (Table 1, entry 3). How-

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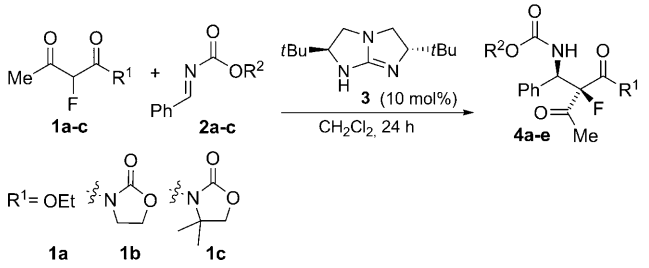
Table 1. Highly enantioselective and diastereoselective Mannich reactions of fluorocarbon nucleophiles **1a–c**.



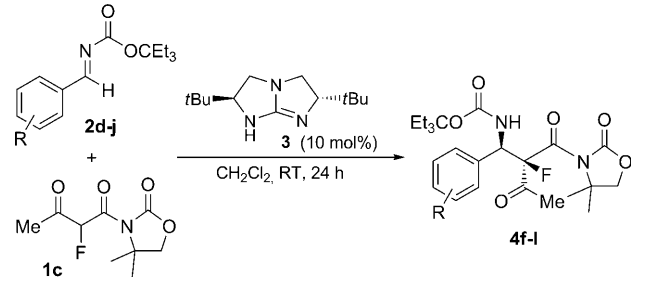
	1	2 [R^2]	T [°C]	4	Yield [%][a]	dr[b]	*ee* [%][c]
1	**1a**	**2a** [Et]	−50	**4a**	99	9:1	84
2	**1a**	**2b** [*t*Bu]	−50	**4b**	90	10:1	71
3	**1b**	**2b** [*t*Bu]	RT	**4c**	92	1:1	83
4	**1c**	**2b** [*t*Bu]	RT	**4d**	85	4:1	95
5	**1c**	**2c** [CEt_3]	RT	**4e**	96	96:4	98

[a] Yield of isolated product. [b] Determined by HPLC analysis. [c] Determined by HPLC.

ever, when β-keto acetyloxazolidinone **1c** was used as the donor with *N*-3-ethylpentan-3-yloxycarbonyl (Eoc) imine **2c** (both developed in our laboratory), we obtained adduct **4e** in excellent yields and excellent enantio- and diastereoselectivities (Table 1, entry 5).

With the optimized conditions established, we evaluated the performance of β-keto acetyloxazolidinone **1c** with a series of different *N*-Eoc imines in the presence of 10 mol% of bicyclic guanidine catalyst **3** (Table 2). Excellent results (up to 98:2 dr, up to 99% *ee*) were observed with imines containing both electron-withdrawing and electron-donating aryl groups. Different substituents on the aryl ring did not affect the *ee* values and diastereoselectivities. β-Keto acyloxazolidinones **1d–g**, which contain different aliphatic chains, were also investigated under the optimized conditions (Table 3). Increasing the length of the donor did not greatly

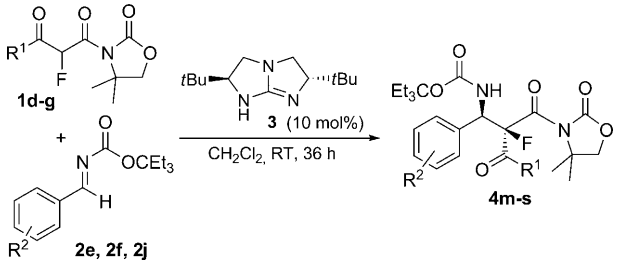
Table 2. Highly enantioselective and diastereoselective reactions between β-keto acetyloxazolidinone **1c** and *N*-Eoc imines.



	2	R	4	Yield [%][a]	dr[b]	*ee* [%][c]
1	**2d**	4-F	**4f**	99	95:5	98
2	**2e**	4-Br	**4g**	99	99:1	98
3	**2f**	3-OMe	**4h**	99	95:5	98
4	**2g**	3-Cl	**4i**	93	93:7	98
5	**2h**	2-Napth	**4j**	99	93:7	98
6[d]	**2i**	4-Cl	**4k**	97	94:6	97
7[d]	**2j**	4-OMe	**4l**	96	98:2	99

[a] Yield of isolated product. [b] Determined by HPLC analysis. [c] Determined by HPLC. [d] Toluene as solvent, RT. 48 h.

Table 3. Highly enantioselective and diastereoselective reactions between β-keto acyloxazolidinone **1d–g** and *N*-Eoc imines.



	1	R^1	2	4	Yield [%][a]	dr[b]	*ee* [%][c]
1	**1d**	*n*Pr	**2e**	**4m**	99	95:5	97
2	**1d**	*n*Pr	**2j**	**4n**	90	97:3	98
3	**1e**	$PhCH_2CH_2$	**2j**	**4o**	92	96:4	98
4	**1f**	Bn	**2e**	**4p**	99	96:4	>99
5	**1f**	Bn	**2f**	**4q**	95	92:8	95
6	**1f**	Bn	**2j**	**4r**	93	94:6	98
7[d]	**1g**	$(CH_3)_2C{=}CH$	**2j**	**4s**	92	98:2	97

[a] Yield of isolated product. [b] Determined by HPLC analysis. [c] Determined by HPLC. [d] Reaction time was 60 h.

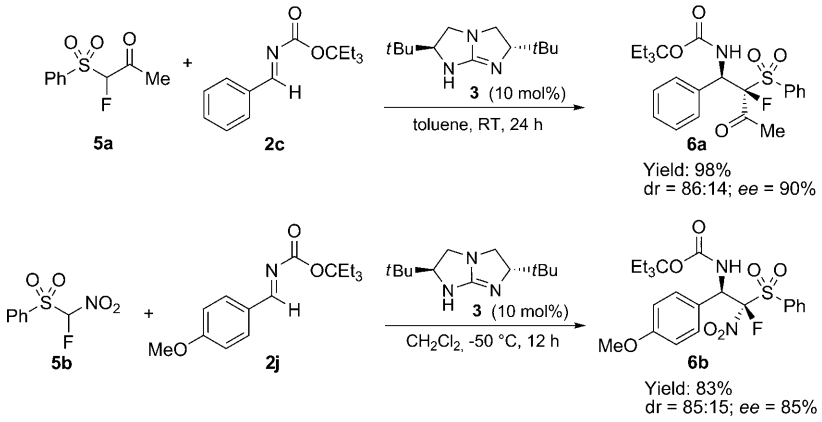
affect either the enantio- or diastereoselectivities, but the reactions became more sluggish and required longer reaction times. Interestingly, dimethyl-ene-keto acetyloxazolidinones **1g** (Table 3, entry 7) also provided excellent results. The presence of the additional double bond in adduct **4s** should allow ample opportunities for further functionalization.

FBSM was shown to be an excellent fluoronucleophile. We prepared α-fluoro-β-sulfones **5a** and **5b** to determine whether they are suitable for this reaction. Indeed, the Mannich reaction of 1-fluoro-1-(phenylsulfonyl)propan-2-one (**5a**) gave an adduct with a high *ee* value and good diastereoselectivity [Eq. (1)].

The preparation of α-fluoro-α,β-diamines, particularly one that contains a quaternary fluorinated carbon, is an attractive target. α-Fluoro-α-nitro(phenylsulfonyl)methane (FNSM; **5b**) was previously shown to participate in Michael reaction with good results.[16b] FNSM and *N*-Eoc imine **2j** underwent Mannich reaction smoothly at −50°C to give adduct **6b** with a good *ee* value and diastereoselectivity [Eq. (2)].

The ability of malonates and β-ketoesters to be decarboxylated via their corresponding acids under acidic conditions after alkylation allows these reagents to be extremely useful and form a significant portion of undergraduate teaching on carbonyl chemistry. It is known that decarboxylation occurs through a six-membered transition state with the elimination of a molecule of carbon dioxide. It is, however, less well known that, under strongly basic conditions, β-ketoesters undergo deacylation, with cleavage of the keto side, in a retro-Claisen condensation fashion. The ability of α,α-dichloro-β-keto esters to react with even relatively weak nucleophiles under mild conditions to effect this deacylation reaction has also been overlooked.[17]

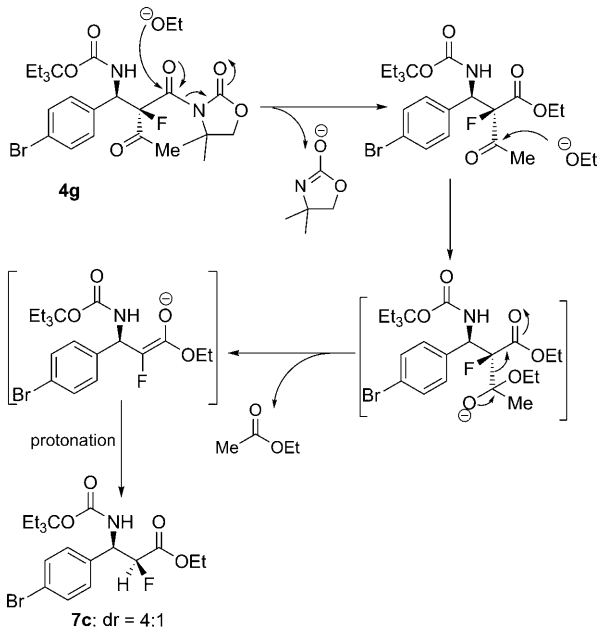
Initially, we were searching for mild conditions to modify the oxazolidinone moiety of the Mannich product. We



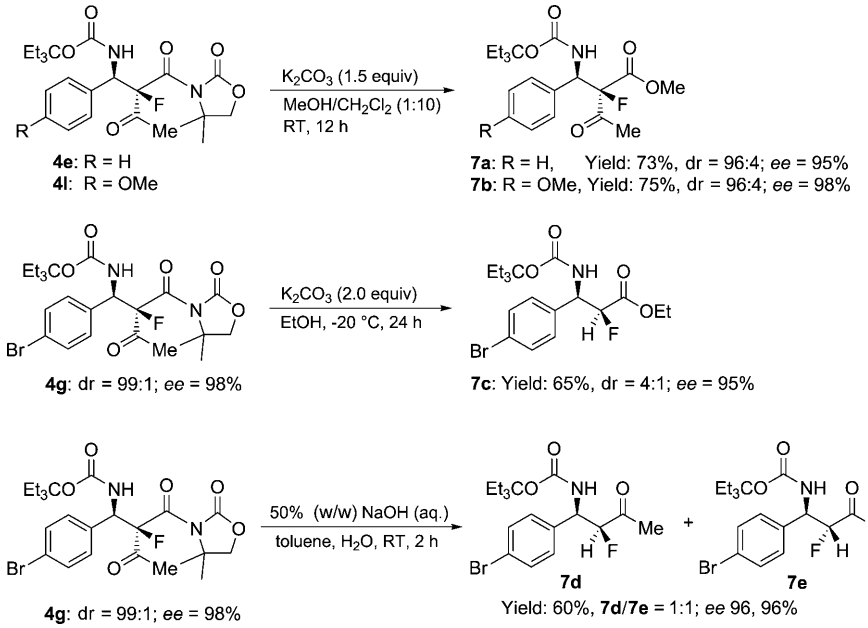
(1)

(2)

found that oxazolidinone can be converted to a methyl ester easily by using potassium carbonate under mild conditions without loss of *ee* value or diastereoselectivity [Eq. (3)]. When the amount of potassium carbonate was increased, transesterification was followed by deacylation to yield the α-fluoro-β-amino ester **7c** [Eq. (4)]. A round of optimization revealed that the use of ethanol at a lower reaction temperature gave the best yield. The deacylation should proceed by retro-Claisen condensation[18] to provide an enolate that undergoes diastereoselective protonation to give the *syn* diastereoisomer as the major product (Scheme 1). When sodium hydroxide was used, the oxazolidinone moiety was converted to the carboxylate salt, which underwent decarboxylation.[19] The enolate subsequently generated underwent protonation to give a 1:1 mixture of α-fluoro-β-amino ketones **7d** and **7e**, which were separated by flash chromatography [Eq. (5), Scheme 2]. The use of such mild conditions for deacylation and decarboxylation is likely to be due to the inductive effect of a neighboring C–F bond.



Scheme 1. Preparation of α-fluoro-β-amino ester **7c** by deacylation and protonation reactions.



(3)

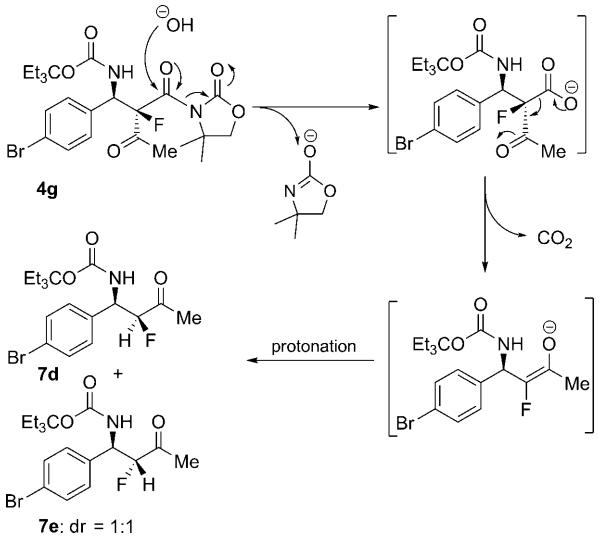
(4)

(5)

tives with chiral fluorinated carbon were obtained through selective deacylation or decarboxylation reactions. A transient enolate was obtained by retro-Claisen or decarboxylation followed by protonation to give enantiopure fluorinated compounds. Such processes constitute new strategies that have not previously been reported.

Experimental Section

Representative procedure: Synthesis of 4e: *N*-3-Ethylpentan-3-yloxycarbonyl (Eoc) imine (**2c**; 24.7 mg,



Scheme 2. Preparation of α-fluoro-β-ketones **7d** and **7e** by deacylation and protonation reactions.

0.1 mmol, 2.0 equiv) and catalyst **3** (1.12 mg, 0.005 mmol, 0.1 equiv) were dissolved in CH_2Cl_2 (0.5 mL), and the mixture was stirred at room temperature for 10 min. Fluorocarbon nucleophile **1c** (10.85 mg, 0.05 mmol, 1.0 equiv) was added, and this reaction mixture was stirred at room temperature for 24 h. After complete consumption of **1c**, the solvent was removed in vacuo, and the crude product was directly loaded onto a short silica gel column. Flash chromatography with hexane/ethyl acetate mixtures led to product **4e** (22.2 mg, 96%) as colorless oil.

Acknowledgements

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Keywords: decarboxylation · fluorocarbon nucleophiles · guanidine · Mannich reaction · retro-Claisen condensation

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