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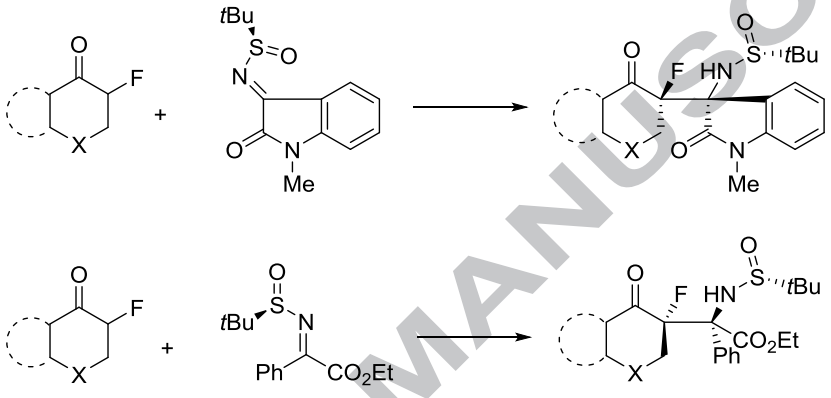

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A diastereoselective Mannich reaction of α-fluoroketones with ketimines: construction of β-fluoroamine motifs with vicinal tetrasubstituted stereocenters

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ABSTRACT

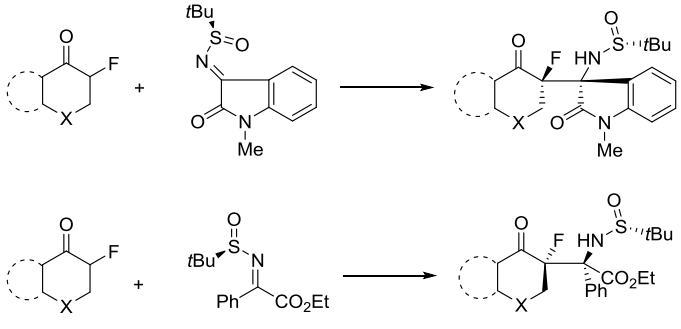
A diastereoselective Mannich reaction has been developed for the synthesis of chiral β-fluoroamine motifs by the reaction of α-fluoroketones with ketimines, including isatin-derived ketimines and phenylglyoxylate-derived ketimines. This method provides a concise route to a variety of biologically important 3-aminooxindoles and α-amino acids featuring fluorine-containing vicinal tetrasubstituted stereocenters.

Introduction

Fluorine is extremely important in medicinal chemistry, as the introduction of fluorine into bioactive molecules can often lead to improved binding affinity, metabolic stability and bioavailability.[1] Nowadays, around 20% of pharmaceuticals on the market contain at least one fluorine atom. In this context, the β-fluoroamine unit is a privileged structural motif which has been found in many bioactive molecules and drug candidates.[2] A fluorine substitution can reduce the basicity of nearby amines, and thus can modulate the pharmacokinetic properties of the molecule and its binding affinity.[3] Therefore, efficient methods providing access to β-fluoroamine motifs are highly valuable.

The syntheses of β-fluoroamine motifs have been reported in numerous publications, and can be divided into two main approaches: fluorination, and use of fluorinated building blocks.[4,5] However, the asymmetric synthesis of β-fluoroamine motifs, especially with fully substituted adjacent stereocenters, remains a formidable challenge.[6,7] There are only a few literature reports that document the construction of chiral β-fluoroamine motifs with tetrasubstituted stereocenters.[7] Among them, the asymmetric condensation of the trisubstituted fluoroenolate of α-fluoroketones with ketimines represents a straightforward approach to such structural motifs. For example, Wang and co-workers described an elegant Mannich reaction of 2-fluoro-1,3-diketone hydrates with isatin-derived ketimines catalyzed by a chiral copper-diamine complex,[7a] while Zhou *et al* developed an enantioselective addition of fluorinated silyl enol ether with cyclic N-sulfonyl ketimines.[7b] While efficient, the use of such activated α-fluoroketone nucleophiles is not green from the perspective of atom economy, and their preparation is difficult compared with that of simple α-fluoroketones.

We have been interested in the use of simple α-fluorocarbonyl compounds to construct stereogenic carbon−fluorine centers.[8] Recently, we have shown that α-fluoroketones are competent fluorocarbon nucleophiles and can undergo highly diastereoselective Mannich reactions with Ellman's aldimines.[9,10] Herein, we disclose the Mannich reaction between α-fluoroketones and isatin-derived ketimines to provide access to β-fluoroamine motifs containing fully substituted adjacent stereocenters (Scheme 1). This method was also extended to ethyl benzoylformate-derived ketimines.



Scheme 1. Construction of β-fluoroamine motifs containing vicinal tetrasubstituted stereocenters

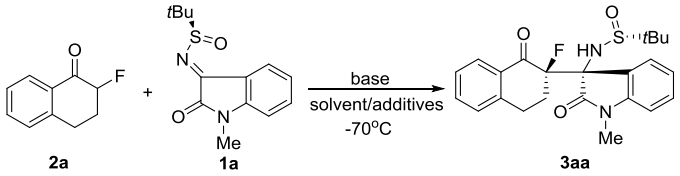
Results and discussion

We initially evaluated isatin-derived ketimine **1a** as a model substrate, as the resulting 3-aminooxindole motifs can be found in a wide range of important pharmaceutical agents and bioactive molecules.[11,12] When **1a** was reacted with 1.2 equivalents of α-fluoroketone **2a** in the presence of NaHMDS, only a trace

amount of the desired Mannich product **3aa** was observed (Table 1, entry 1). The use of KHMDS as base gave a good yield, but with low diastereoselectivity (entry 2 and 3). When LiHMDS was used, **3aa** was obtained in 82% yield, with an improved diastereoselectivity of 60:40:0:0 (entry 4). The reaction solvent was then screened; DMF proved to be an unsuitable solvent (13% yield, entry 5), while DCM and toluene gave comparable yields and diastereoselectivities (entries 6 and 7). The inclusion of additives was also evaluated. While HMPA inhibited the reaction almost completely (entry 8), a beneficial effect was observed when TMEDA was used (entries 9 and 10). Optimal reaction conditions involving a combination of toluene and TMEDA gave the product **3aa** in 95% yield and synthetically useful diastereoselectivity (d.r. = 72:28:0:0) (entry 10).

Table 1

Optimization of the addition of α-fluoroketone **2a** to isatin-derived imine **1a**[a]



entry	base	Solvent/additive	Yield (%)[b]	d.r.[c]
1	NaHMDS	THF	<5	N[d]
2	KHMDS	THF	70	51:49:0:0
3	KHMDS	toluene	56	57:43:0:0
4	LiHMDS	THF	82	60:40:0:0
5	LiHMDS	DMF	13	N[d]
6	LiHMDS	DCM	80	57:43:0:0
7	LiHMDS	toluene	85	60:40:0:0
8	LiHMDS	toluene/HMPA (v/v=10/1)	<5	N[d]
9	LiHMDS	THF/TMEDA (v/v=10/1)	85	60:40:0:0
10	LiHMDS	toluene/TMEDA (v/v=10/1)	95	72:28:0:0

[a] Reaction conditions: under a N_2 atmosphere, the base (0.6 mL, 1.0 mol/L in THF) was added slowly to a reaction mixture of **1a** (0.5 mmol), and **2a** (0.6 mmol) in the specified solvent/additive (3.0 mL) at −70 °C.

[b] Yields refer to isolated yields of the stereoisomers.

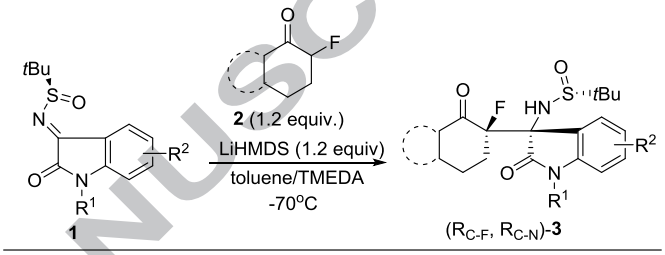
[c] d.r. Determined by ^{19}F NMR or ^{1}H NMR spectroscopy on the crude products.

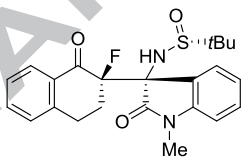
[d] Not determined.

We then investigated the substrate scope of the reaction with regard to isatin-derived ketimines, and the results are summarized in Table 2. As shown, steric interactions between the reactants played an important role in dictating the efficiency of the reaction, as exemplified by the 1-, 4- , 5-, and 6-substituted ketimines **1b**–**1i**, which gave a lower yield due to the incomplete conversation of the ketimines. The electronic nature of the substituents also has impact on the outcome of the reaction. For example, 4-methyl ketimine **1b** seems to work well under the reaction conditions, giving **3ab** in a very good diastereoselectivity (d.r. = 94:6:0:0), whereas a decreased diastereoselectivity (**3ac**, d.r. = 81:19:0:0) was obtained when the 4-bromo substrate **1c** was used. The 5-substituted substrates **1d**–**1e** also worked with similar efficiency to successfully give products **3ad**–**3ae** in good yields; the electron-donating 5-methyl substituent **3ad** gave a higher diastereoselectivity (d.r. = 88:6:6:0), compared with that of the 5-chloro substituent **3ae** (d.r. = 70:30:0:0). The 6-chloro ketimine **1f** also afforded the product **3af** in a very good yield as a 67:26:7:0 mixture of diastereoisomers. The influence of the N-substituent on the outcome of reaction was also evaluated. N-Allyl, N-benzyl and N-CPh_3 derivatives **1g**–**1i** were all tolerated, giving the desired products **3ag**–**3ai** in good yields. Importantly, compared with the N-CH_3 substrate **1a**, the bulky N–CPh_3 group proved to be beneficial to the stereoselectivity of the reaction, with **3ai** being formed with a 90:10:0:0 diastereoselectivity. The 5-fluoro-6,7-dihydrobenzo*[b]*thiophen-4(5H)-one **2b** and 3-fluorochroman-4-one **2c** were also successfully reacted to give **3bi** (71%, d.r. = 71:29:0:0) and **3ca** (65%. d.r. = 45:33:17:5). It is worth noting that for each substrate, the major diastereomer could be easily separated from the crude products through routine flash column chromatography.

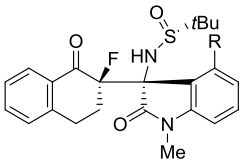
Table 2

The diastereoselective addition of α-fluoroketones **2** to isatin-derived ketimines **1**[a,b]



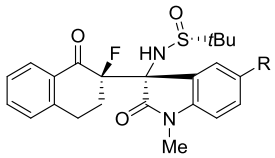


3aa, 95%, d.r.= 72:28:0:0



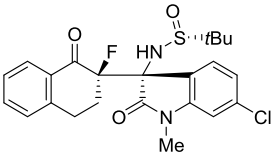
3ab, R = CH_3, 72%, d.r.= 94:6:0:0

3ac, R = Br, 76%, d.r.= 81:19:0:0

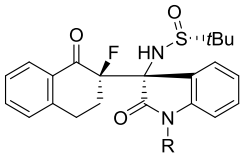


3ad, R = CH_3, 80%, d.r.= 88:6:6:0

3ae, R = Cl, 73%, d.r.= 70:30:0:0



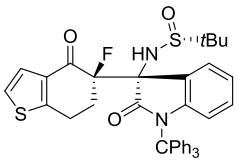
3af, 78%, d.r.= 67:26:7:0



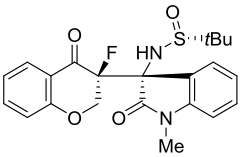
3ag, R = allyl, 84%, d.r.= 67:33:0:0, *x-ray*

3ah, R = Bn, 77%, d.r.= 67:33:0:0

3ai, R = CPh_3, 72%, d.r.= 90:10:0:0



3bi, 71%, d.r.= 71:29:0:0



3ca, 65%, d.r.= 45:33:17:5

[a] The yields refer to isolated yields of the two or three stereoisomers.

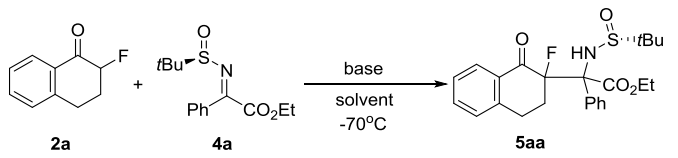
[b] d. r. determined by ^{19}F NMR or ^{1}H NMR spectroscopy.

Phenylglyoxylate-derived ketimines are important building blocks and have been frequently used in the synthesis of chiral α-amino acids bearing a tetrasubstituted carbon.[13] Thus, we wished to develop a method to synthesize α-amino acids with fluorine-containing vicinal tetrasubstituted stereocenters. However, when **4a** was reacted with **2a** under the reaction conditions used in Table 2, the Mannich product **5aa** was not observed (Table 3, entry 1). Switching the base to NaHMDS only gave a trace amount of **5aa** (entry 3). The reaction proved to work well when

KHMDS was used (entries 4 and 5). Optimal reaction conditions involving KHMDS as base in toluene gave **5aa** in 85% yield with 97:3:0:0 diastereoselectivity (entry 4). The current reaction can be carried out on a gram scale (3 mmol), yielding **5aa** in a comparable yield (1.12 g, 84% yield, 96:4:0:0 dr).

We then investigated other α-fluorinated ketones in this reaction. As shown in Table 4, the α-fluoroketones **2b**–**2d** were competent nucleophiles and gave the Mannich products **5ab**–**5ad** in moderate to good yields, with moderate diastereoselectivities. Of note, the 5-fluoro-6,7-dihydrobenzo[b]thiophen-4(5H)-one **2b** worked well under the reaction conditions, giving **5ab** in a good yield (82%). The 3-fluorochroman-4-one **2c** and **2d** also reacted smoothly to give the corresponding products **5ac** and **5ad**, albeit in a lower diastereoselectivity (75:25:0:0 and 75:17:8:0 respectively).

Table 3
Optimization of the addition of α-fluoroketone **2a** to phenylglyoxylate-derived imine **4a**[a]

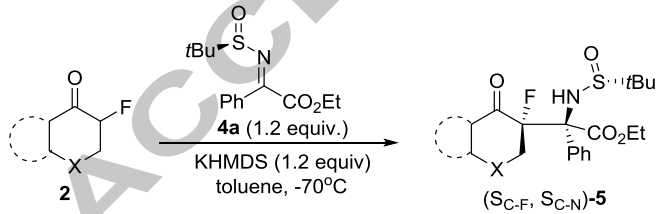


2a **4a** **5aa**

entry	base	Solvent	Yield (%)[b]	d.r.[c]
1	LiHMDS	toluene/TMEDA (v/v=10:1)	0	N[d]
2	LiMDS	toluene	trace	N[d]
3	NaHMDS	toluene	trace	N[d]
4	KHMDS	toluene	85	97:3:0:0
5	KHMDS	THF	55	N[d]

[a] Reaction conditions: under a N_2 atmosphere, the base (0.6 mL, 1.0 mol/L in THF) was added slowly to a reaction mixture of **2a** (0.5 mmol), and **4a** (0.6 mmol) in the specified solvent/additive (3.0 mL) at −70 °C.
[b] Yields refer to isolated yields of the major stereoisomers.
[c] d.r. Determined by ^{19}F NMR spectroscopy on the crude products.
[d] Not determined.

Table 4
The diastereoselective addition of α-fluoroketones **2** to phenylglyoxylate-derived ketimines **4**[a,b]



2 $(S_{C\text{-}F}, S_{C\text{-}N})$-**5**

5aa, 85%, d.r. = 97:3:0:0, *x-ray*

5ab, 82%, d.r. = 87:13:0:0

5ac, 70%, d.r. = 75:25:0:0

5ad, 64%, d.r. = 75:17:8:0

[a] The yields refer to isolated yields of the two or three stereoisomers.
[b] d. r. Determined by ^{19}F NMR spectroscopy.

The absolute configurations of **3ag** and **5aa** were determined by single-crystal X-ray analysis,[14] and compounds **3** and **5** were thus assigned by analogy. Notably, the absolute configuration of the β-fluoroamine motifs in compound ($R_{C\text{-}F}$, $R_{C\text{-}N}$)-**3** is the opposite compared with that in the Mannich product ($S_{C\text{-}F}$, $S_{C\text{-}N}$)-**5**. These results showed that different transition states were involved in the reactions of isatin-derived ketimines **1** and phenylglyoxylate-derived ketimines **4** with α-fluoroketones **2**. The stereoselectivity observed for compound **3** was tentatively explained based on an open transition state (Fig. 1a). The sulfinyl unit and the C=N bond is proposed to adopt an s-cis arrangement, and the Z-enolate of fluoroketone would attack the sterically less hindered Si face of isatin-derived ketimines **1** in an antiperiplanar fashion to give the observed stereoselectivity. For the stereochemical outcome of compound **5**, a chair-like transition state is proposed where the potassium is coordinated to the nitrogen atom and the C=O oxygen atom of phenylglyoxylate-derived ketimine **4** (Fig. 1b).

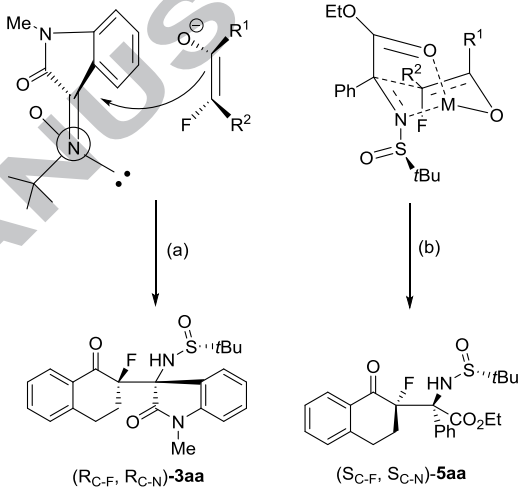
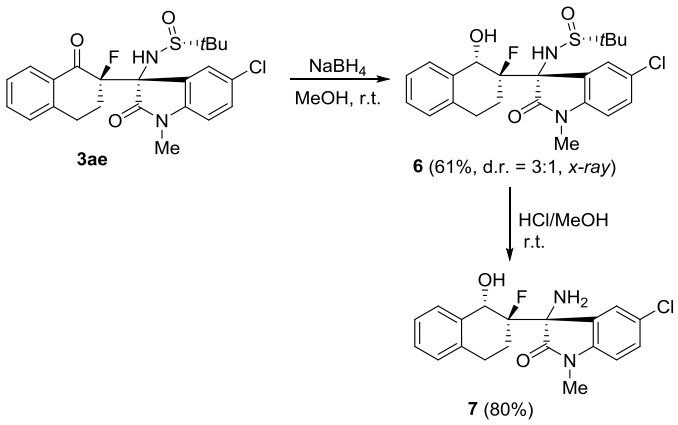


Fig. 1. (a) Open transition-state mode proposed for the diastereoselective addition of α-fluoroketones **2** to isatin-derived ketimines **1**; (b) Closed transition-state mode proposed for the diastereoselective addition of α-fluoroketones **2** to phenylglyoxylate-derived ketimines **4**.

To demonstrate the utility of the method, some elaboration of the obtained products **3** was performed. As shown in Scheme 2, compound **3ae** was subjected to the $NaBH_4$ C=O reduction to give compound **6** in 61% yield and with 3:1 diastereoselectivity. The configuration of compound **6** was confirmed by single-crystal X-ray analysis.[14] Treatment of compound **6** with HCl/MeOH afforded the corresponding compound **7** as a single diastereomer in 80% yield.



3ae **6** (61%, d.r. = 3:1, *x-ray*) **7** (80%)

Scheme 2. Elaboration of compound **3ae**

Conclusions

In summary, we have developed a diastereoselective Mannich reaction of α-fluoroketones and ketimines. Isatin-derived ketimines and phenylglyoxylate-derived ketimines are competent substrates for this reaction, affording 3-aminooxindoles and α-amino acids bearing fluorine-containing vicinal tetrasubstituted stereocenters. This new process represents a viable approach for the syntheses of diverse fluorinated compounds bearing a fully substituted fluorinated carbon center.

Acknowledgements

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14 CCDC 1812528 (**3ag**), 1812299 (**5aa**) and 1818742 (**6**) contain the supplementary crystallographic data for this paper.

Highlights

- The Mannich reaction of simple α-fluoroketones with ketimines was described.
- Isatin-derived ketimines and phenylglyoxylate-derived ketimines were used.
- β-Fluoroamine motifs with vicinal tetrasubstituted stereocenters were obtained.
- Open- and closed transition-state modes were proposed.