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Direct Access to Chiral β-Fluoroamines with Quaternary Stereogenic Center via Cooperative Cation Binding Catalysis

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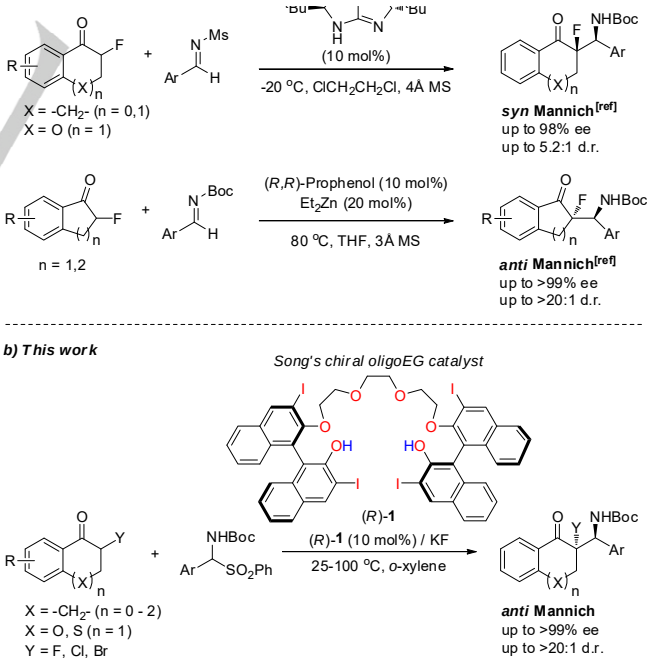
Abstract: *Reported herein is a direct route for chiral β-fluoroamines possessing tetrasubstituted C-F centers through the organocatalytic Mannich reaction of α-fluoro cyclic ketones and α-amidosulfones using a chiral oligoEG as a cation binding catalyst with KF as a base. In most substrates, nearly perfect enantioselectivites were achieved even at very high temperatures (>80 °C). The salient features of this process include (a) a transition metal free and operationally simple procedure, (b) direct use of α-amidosulfones as bench-stable precursors of sensitive imines, (c) direct enolization of racemic α-fluoro cyclic ketones and (d) excellent stereoselectivity up to 99% ee and >20:1 diastereoselectivity (anti:syn). Thus, this protocol is easily scalable and provides a new approach for the syntheses of some biologically relevant products possessing tetrasubstituted C-F centers. Futhermore, this protocol was also successfully extended to generate C-Cl and C-Br quaternary stereogenic centers.*

Fluorine incorporated molecules have received a great deal of interest in life sciences.[1] Due to the higher electronegativity and oxidation potential of the fluorine atom, it can improve the pharmacological properties of a bioactive molecule by altering its lipophilicity, metabolic stability and bioavailability compared to the non-fluorinated parent compound.[1] Indeed, a nearly 20% increase in the number of fluorinated drugs have occurred in the market during the last decade.[2] Consequently, fluorinated analogues of bioactive molecules are now important tools in pharmaceutical research. Among them, molecules containing β-fluoroamine moieties are of great importance in medicinal chemistry due to their privileged structural motif.[3] It is well known that the presence of fluorine at the β-position lowers the pK_a of neighbouring amines, thus enhancing binding interactions and improving metabolic stability. This leads to increased penetration through the central nervous system (CNS) of a biological system.[4] As a consequence, the discovery of a new method for the synthesis of chiral β-fluoroamine derivatives is one of the rapidly growing research areas for synthetic chemists.[5] In particular, chiral β-fluoroamine compounds with quaternary stereogenic C-F centers[6] are expected to have very interesting pharmaceutical properties. In view of this challenging task, very recently, Tan[7a], Trost[7b] and their co-workers utilized catalytic asymmetric Mannich reactions with α-fluoro cycloketones and aromatic aldimines to construct β-fluoroamines with quaternary C-F stereocenters (Scheme 1a).[8] Tan *et.al* successfully utilized chiral guanidine as an organocatalyst to afford chiral β-fluoramine derivatives with the "*syn*" diastereomer as the major product.[7a] Complementary to this work, quite recently, Trost and co-workers utilized the dinuclear Zn/Prophenol catalyst for direct Mannich reaction to furnish highly entio-enriched β-fluoroamines with "*anti*" diastereoselectivity.[7b]

We recently developed[9] chiral oligoEG catalysts **1** as cooperative cation binding catalysts[10] and successfully applied them to a desilylative kinetic resolution of silyl protected secondary alcohols,[9e] asymmetric Strecker synthesis of α-aminoacids,[9d] and kinetic resolution of β-sulfonyl ketones through enantioselective β-elimination.[9f] In continuation of our research on exploring other challenging catalytic asymmetric reactions using **1** (in Scheme 1b), we wished to develop direct catalytic enantioselective Mannich reactions, allowing direct use of α-fluoro cyclic ketones as donors together with α-amidosulfones[11] instead of sensitive corresponding imines, as well as directly affording β-amino α-fluoro cyclic ketones possessing tetrasubstituted C-F centers. We believed that our cation binding catalyst system was ideally suited for this reaction, in which potassium fluoride, upon activation by the chiral cation-binding catalyst, would enable the generation of the corresponding imine substrate *in situ* from α-amidosulfones as well as the enolate substrate *in situ* from ketones. Subsequently, the catalyst would bring both activated reacting partners together in proximity, resulting in a product with high asymmetric induction.



Scheme 1. Enantioselective synthesis of β-fluoroamines with quaternary stereogenic C-F center

Here, we report a transition metal free straightforward route to highly enantio- and diastereo-enriched β-fluoroamine derivatives possessing quaternary C-F centers through direct organocatalytic

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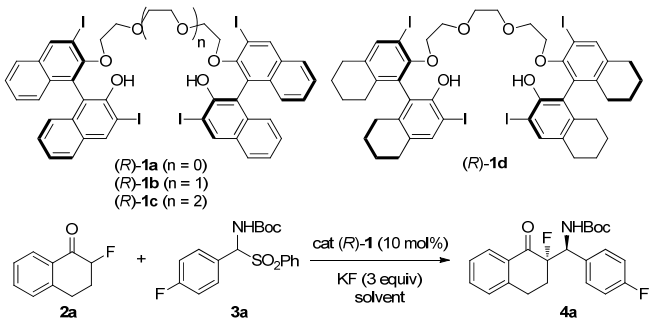
Mannich reaction with α-fluoroketones and α-amidosulfones using a cation-binding catalyst (Scheme 1b). Excellent enantio- and diastereoselectivity was obtained with a variety of fluoro cyclic ketones and α-amidosulfones even at very high temperatures (>80 °C). This protocol was also successfully extended to generate C-Cl and C-Br quaternary stereogenic centers.

Table 1. Optimization of reaction condition

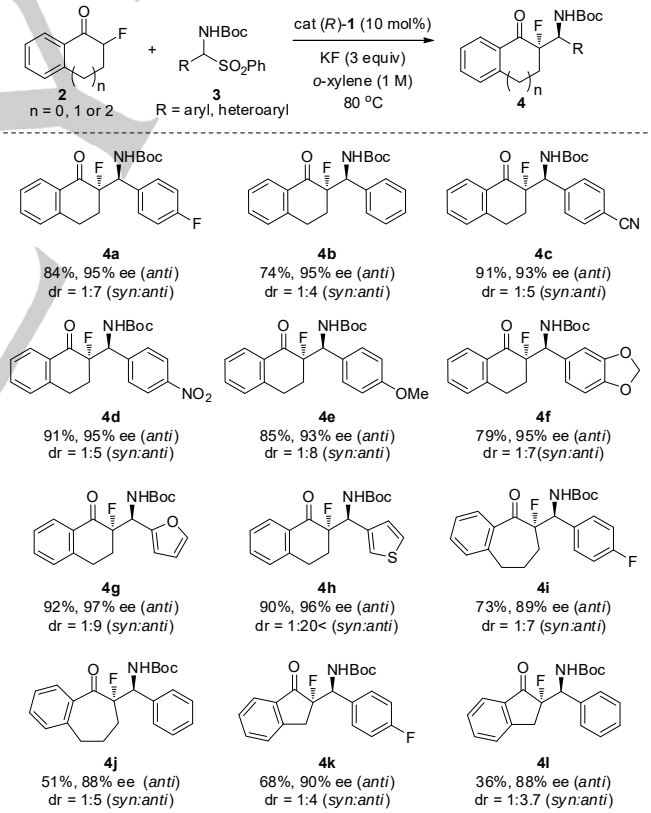


Entry	Catalyst	Solvent	**2** [M]	Time [h]	Temp. [°C]	Conv. [%][b]	*ee* [%][c]	dr[d]
1	(*R*)-**1a**	toluene	0.1	66	rt	30	85	1:7
2	(*R*)-**1b**	toluene	0.1	48	rt	21	>99	n.d.[e]
3	(*R*)-**1c**	toluene	0.1	48	rt	12	0	n.d.
4	(*R*)-**1d**	toluene	0.1	48	rt	9	96	n.d.
5	(*R*)-**1b**	THF	0.1	48	rt	10	89	n.d.
6	(*R*)-**1b**	dioxane	0.1	48	rt	14	99	n.d.
7	(*R*)-**1b**	CH_2Cl_2	0.1	48	rt	20	99	n.d.
8	(*R*)-**1b**	*o*-xylene	0.1	48	rt	54	99	n.d.
9	(*R*)-**1b**	*o*-xylene	0.1	50	70	74	99	1:5
10	(*R*)-**1b**	*o*-xylene	0.25	50	70	96	>99	1:10
11	(*R*)-**1b**	*o*-xylene	1.0	24	80	98	95	1:7
12	(*R*)-**1b**	*o*-xylene	1.0	20	100	100	94	1:5

[a] Unless otherwise indicated, reactions were performed with **2a** (0.1 mmol), **3a** (0.15 mmol), KF (3 equiv.) and catalyst (*R*)-**1** (10 mol%). [b] Conversion was determined by ^{1}H NMR integration. [c] The % *ee* was determined by HPLC analysis using a chiral stationary phase. [d] The relative and absolute configuration of the major diasteromer was unambiguously assigned as "*anti*" and [$(S)_{C\text{-}F}$, $(S)_{C\text{-}NHBoc}$], respectively, by comparison of the coupling constant and the retention time of HPLC with the literature data.[7b] [e] not determined.

Our initial investigation of the asymmetric Mannich reaction of α-amidosulfone **3a** with α-fluorotetralone **2a** as a model substrate is summarized in Table 1. The effect of the catalyst structure ((*R*)-**1a-d**) on the reaction outcome was first investigated with a catalyst loading of 10 mol% in toluene at room temperature. As we expected, based on our knowledge of the catalytic performance of chiral oligoEGs **1a-1d**,[9] catalyst **1b** was found to be the best in terms of the enantioselectivity of the major diastereomer (99% *ee*, entry 2). In further experiments, different solvents were examined (entry 2 and entries 5-8). Toluene and xylenes proved to be the optimal choice. In non-polar solvents such as toluene and *o*-xylene, 54% of starting material **2** (Table 1, Entries 2 and 8) was converted after 48 h to product with 99% *ee*, whereas in polar aprotic solvents (Table 1, entries 5-7), <30% conversion was attained even after running the reaction for more than 48 h. Although we observed the formation of the desired Mannich product with perfect enantiopurity (>99% *ee*), the reaction proceeded too slowly (Table 1, entries 2 and 8). To improve the % conversion, we next attempted different conditions by changing the reaction temperature and concentration. Upon further optimization, we were pleased to observe that an increase in the reaction rate was paralleled by an increase in temperature and concentration without diminishing the enatioselectivity or the diastereoselectivity (entries 9-11). Finally, at 80 °C and in very high concentration (1 M), the reaction proceeded with full conversion (84% isolated yield) within 24 h, with excellent enantioselectivity (95% *ee*) and the diastereoselectivity (1:7 for *anti*) (entry 11).[12] Further increase in the temperature to 100 °C showed only a comparable decrement in enantioselectivity to 94% *ee*, indicating a relatively high stability for the transition state (entry 12).

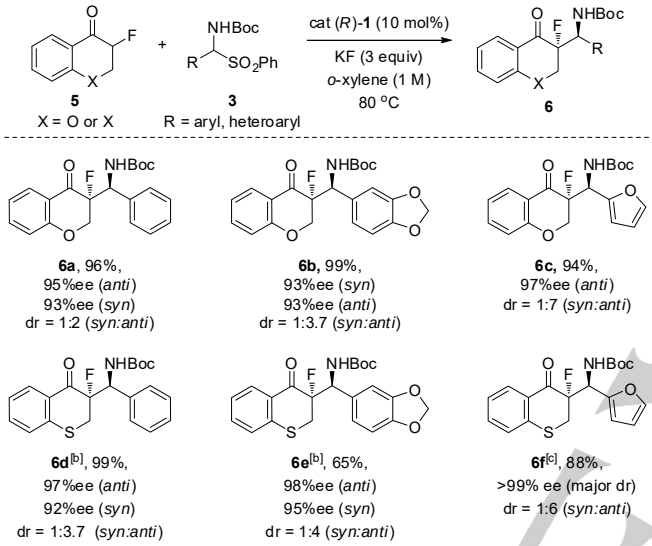
With the optimal catalytic conditions in hand, we then evaluated the generality of our protocol with α-amidosulfones as the electrophilic partner. As shown in Scheme 2, a variety of aromatic and heteroaromatic Boc-α-amidosulfones were successfully reacted with racemic α-fluoro cyclic ketones **2** in the presence of KF (3 equiv.) and catalyst (*R*)-**1b** (10 mol%) in *o*-xylene (1 M). Regardless of the electronic and steric nature of the substituents on the aromatic ring, all α-amidosulfones **3** as imine precursors tested in this study were smoothly converted to the corresponding Mannich products **4a-4j** in excellent yields and almost perfect *ee*s. Heteroaromatic substrates such as 3-furyl (**4g**) and 3-thienyl (**4h**) also gave excellent yields and stereoselectivities (Scheme 2).



Scheme 2. Substrate scope for the Mannich reaction of **2** to α-amidosulfone **3**.[a] [a] Reactions were performed with **2** (0.3 mmol), **3** (0.45 mmol), and (*R*)-**1b** (10 mol%) in *o*-xylene (1M) at 80 °C for 24 h (in case of **4a-d**), 36 h (in case of **4e**) . The yield was determined after chromatographic purification, and the % *ee* was determined by HPLC analysis using a chiral stationary phase. Diastereomeric ratio was determined by ^{1}H NMR.

We then investigated other types of α-fluorocyclic cyclic ketones with five to seven membered carbocyclic rings for this reaction. As shown in Scheme 2, fluorobenzosuberones **2** (n = 2) and fluoroindanones (n = 0) also proved to be excellent Mannich donors, furnishing the Mannich product **4i-4l** in high to excellent enantioselectivity (88 to 95% *ee*).[13]

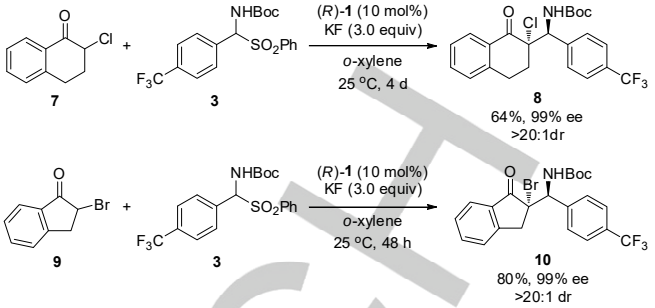
The substrate scope was also successfully extended to chromanones and thiochromanones, which are present in many biologically active natural compounds.[14] α-Fluorochromanones and α-fluorothiochromanones were smoothly converted to the corresponding Mannich products **6a-f** together with excellent enantioselectivity (up to 99% ee for major diastereomer) and reasonable diastereomeric ratio (up to 7:1 for *anti*) (Scheme 3).



Scheme 3. Substrate scope for the Mannich reaction of **5** to α-amidosulfone 3.[a] [a] Reactions were performed with **5** (0.3 mmol), **3** (0.45 mmol), and (*R*)-**1b** (10 mol%) in *o*-xylene (1M) at 80 °C for 28 h. [b] Reactions were performed with **5** (0.2 mmol), **3** (0.3 mmol), and (*R*)-**1b** (10 mol%) in *o*-xylene (1M) at 70 °C for 36 h. [c] Reactions were performed with **5** (0.3 mmol), **3** (0.45 mmol), and (*R*)-**1b** (10 mol%) in *o*-xylene (1M) at 70 °C for 28 h.

We were further interested in expanding our optimized catalytic condition to the Mannich reaction of other halogenated cyclic ketones such as **7** and **9** to generate C-Cl and C-Br quaternary stereogenic centers[15] in the corresponding products, respectively. The preliminary results of this significant transformation are as shown in Scheme 4. Delightfully, both the ketones **7** and **9** furnished the Mannich products **8** and **10**, respectively, in quantitative yield with almost perfect enantio- and diastereoselectivity at room temperature (Scheme 4).

Based on our experimental results and our previous reports regarding cation binding catalysis, the plausible reaction mechanism is illustrated in Figure 1. At the first step, **complex I** is formed by the complexation of KF with the catalyst, which then engages with amidosulfone to form the **complex II**. Subsequently, elimination of the sulfinate group from amidosulfone affords an imine activated through hydrogen bonding as dictated in **complex III**. The subsequent coordination of potassium enolate (generated in-situ from cyclic ketones with KF) to the catalyst is followed by its addition to the imine to provide the enantio- and diastereo-enriched adducts (up to 99% ee



Scheme 4. Mannich reaction of **7** or **8** to α-amidosulfone 3.[a] [a] Reactions were performed with **7** or **8** (0.5 mmol), **3** (1.5 equiv.), and (*R*)-**1** (10 mol%) in *o*-xylene (5.0 mL) at 25 °C.

and up to >20:1 d.r. (*anti:syn*)). As shown in the proposed mechanism, the cation (K^+)-binding to the catalyst is critical to induce high reactivity and high enantioselectivity in the enantio-determining step by the formation of the chiral cage. To support this proposed reaction mechanism, we conducted an in situ electrospray ionization mass spectroscopy (ESI-MS) analysis of the reaction mixture (see the Supporting Information). Gratifyingly, some proposed intermediates could be seen in the measurements of ESI-MS (positive ion mode). The signals at *m/z* 1228.8168, *m/z* 1593.7529, *m/z* 1451.9171 and *m/z* 1614.1870 correspond to [**I** − F^-], [**II** − F^-], [**III** − $PhSO_2^-$] and [**IV**], respectively.

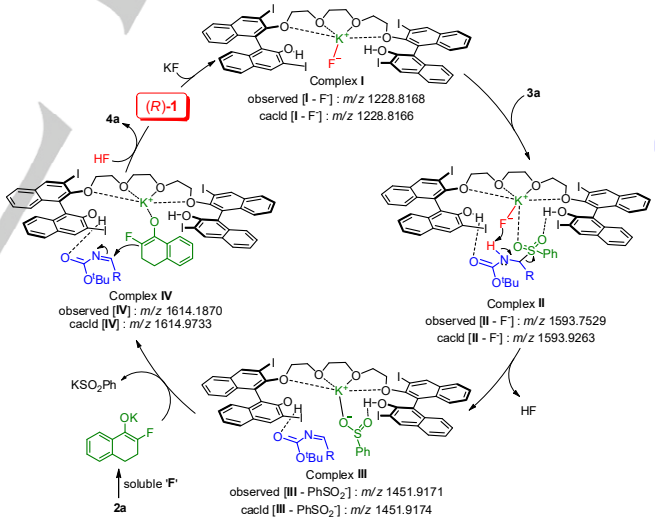


Figure 1. A proposed reaction mechanism and observation of the intermediates

In summary, we have developed a transition metal free straightforward strategy for the synthesis of highly enantio- and diastereo-enriched β-fluoroamine derivatives possessing quaternary C-F centers through direct organocatalytic Mannich reactions with fluoroketones and α-amidosulfones using a cation-binding catalyst and KF as a base. Excellent enantio- and diastereoselectivity were obtained with a variety of fluoro cyclic ketones and α-amidosulfones even at a very high temperature (80 °C), perhaps due to the conformational stability of the transition state. The salient features of this process

include (a) a transition metal free and operationally simple procedure, (b) direct use of α-amidosulfones as bench-stable precursors of sensitive imines, enabling the use of a broad scope of α-amidosulfones, (c) direct enolization of racemic α-fluoro cyclic ketones and (d) excellent stereoselectivity with up to 99% *ee* and >20:1 diastereoselectivity (*anti*:*syn*). This protocol was also successfully extended to generate C-Cl and C-Br quaternary stereogenic centers. Thus, we believe that this protocol can provide a new approach for the syntheses of diverse biologically relevant products possessing quaternary stereogenic C-halogen centers. The extension of this strategy to the synthesis of quaternary carbon in acyclic systems is currently underway in our laboratory.

Acknowledgements

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Keywords: cation-binding catalysis • chiral oligoethylene glycol catalyst • Mannich reaction • β-fuoroamines • quaternary stereogenic center

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[12] Instead of α-amido sulfone **3a**, the direct use of the corresponding imine gave comparable catalytic results. The product **4a** was obtained in 67% yield with 92% ee for *anti*-diastereomer (dr = 1:7 for *syn : anti*).

[13] However, acyclic α-fluoroketones such as 2-fluoro-1-phenylpropan-1-one and 2-fluoro-3-methyl-1-phenylbutan-1-one did not undergo the reaction under the same conditions.

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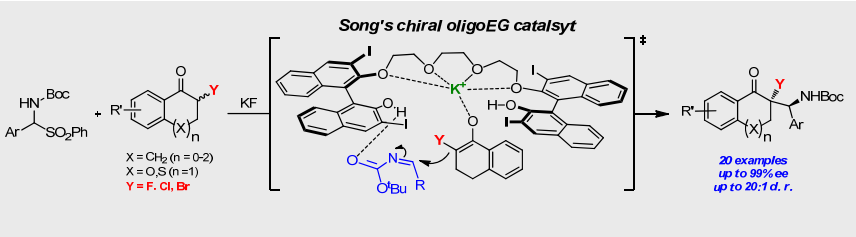

V. Vaithiyanathan, M. J. Kim Y. Liu, H. Yan and C. E. Song**

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Direct Access to Chiral β-Fluoroamines with Quaternary Stereogenic Center via Cooperative Cation Binding Catalysis

A highly efficient asymmetric Mannich reaction of α-fluoro cyclic ketones with α-amidosulfones as the imine surrogates, affording β-fluoroamines possessing quaternary stereogenic C-F center in excellent stereoselectivity (up to 99% ee and up to >20:1 d.r. (*anti:syn*)), is achieved by using a Song's chiral oligoEG as a cation binding catalyst and KF as a base. Catalysis in a confined chiral cage, generated in-situ by binding the potassium cation with the polyether backbone is the key factor in inducing high reactivity and enantioselectivity.