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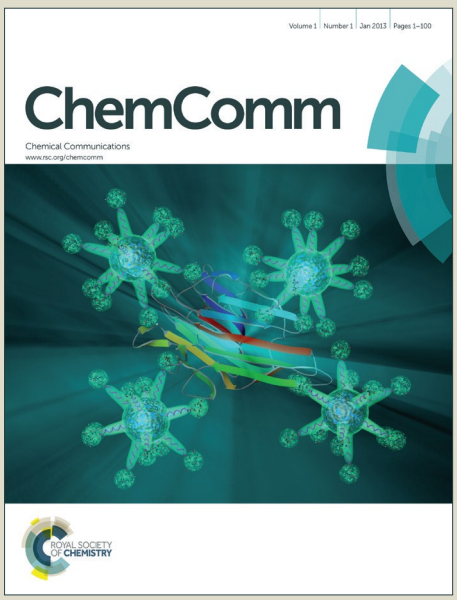

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ARTICLE TYPE

Asymmetric synthesis of quaternary α-fluoro-β-keto-amines via detrifluoroacetylative Mannich reactions

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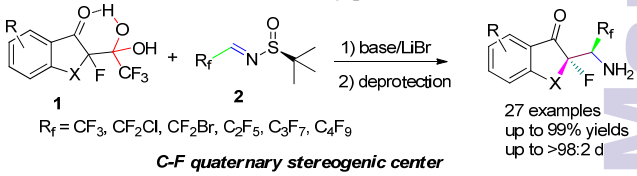
An efficient asymmetric detrifluoroacetylative Mannich addition reactions between 2-fluoro-1,3-di-ketones/hydrates and chiral *N*-sulfinyl-imines via C-C bond cleavage were reported, which afforded C-F quaternary α-fluoro-β-keto-amines with excellent yields and high diastereoselectivity.

Current interest in the organo-fluorine chemistry is at all-time high due to the ever-growing role of fluorine-containing compounds in the design of new pharmaceuticals and agrochemicals.[1,2] During the last decade, particular attention has been focused on the asymmetric synthesis of various fluorinated molecules due to the known relevance of chirality to biological activity.[3,4] Thus, numerous practical methods have been developed allowing biological evaluation of the target fluorinated compounds in enantiomerically pure form.[5,6] However, some areas of asymmetric organo-fluorine methodology are lacking practical solutions. For example, among the marketed drugs, the number of compounds possessing quaternary C-F stereogenic center is rather small clearly corresponding to the synthetic challenge associated with preparation of these compounds in enantiopure form.[1] One of the apparent achievements in this area is the catalytic asymmetric "electrophilic" fluorination, where remarkable synthetic breakthroughs have been reported.[7,8] Nevertheless, this approach allows preparation of structurally limited C-F compound leaving this area open for new methodological developments. In particular, quaternary α-fluoro-β-keto-amines represent an attractive class of substrates with proven pharmaceutical potential.[1-4] A number of elegant catalytic approaches have been reported to access the basic α-fluoro-β-keto-amino structural unit.[9] However, the common shortcoming of these methods is generally low control of the relative stereochemistry necessitating hard purifications of diastereomeric products. Furthermore, the enantioselectivity of the reactions, though promising, is still far from synthetically useful levels. Consequently, there is no example on synthesis of α-fluoro-β-keto-amino compound reported in diastereo- and enantiomerically pure form until now. Since the asymmetric catalytic approaches clearly need profound redesigning and refining, we trust that the development of facile stoichiometric methods are extremely desirable to satisfy the apparent need in optically pure compounds of this type for wide-ranging biological studies. Herein we report detrifluoroacetylative Mannich reactions between keto-hydrates **1** (Scheme 1) and chiral imines **2** providing a practical access to α-fluoro-β-keto-amino compounds **3** in diastereo- and enantiomerically pure form.



Scheme 1 Asymmetric synthesis of compounds with C-F quaternary stereogenic centers.

Following our continuous interest in the methodology developed for the synthesis of biologically relevant fluorine containing compounds,[10-12] we are currently engaged in two actively pursued projects. One is exploration of the chemistry of (*R*)- and (*S*)-*N*-*tert*-butanesulfinyl (3,3,3)-trifluoroacetaldimine **2a**[13,14], as a reagent for installation of the pharmacophoric 2,2,2-trifluoro-1-(amino)ethyl [CF_3–$CH(NH_2)$-] moiety.[15] The other is novel detrifluoroacetylative in situ generation of fluoro-enolates[16] and their asymmetric aldol and Mannich addition reactions.[17] Based on our experience,[17,18] we speculated that detrifluoroacetylative Mannich additions of **2a** with newly developed type of keto-hydrates **1** would be a straightforward approach to the quaternary α-fluoro-β-keto-amino compounds.

First, we conducted the optimization study to estimate the synthetic potential and level of stereoselectivity, and the results are shown in Table 1. The initial reaction conducted in THF using TEA as a base, readily took place at ambient temperature furnishing the product **3aa** in 95% yield and excellent diastereoselectivity (92:8 dr, entry 1). Screening several other organic bases, such as DABCO (entry 2), Hünig's base[19] (DIPEA, entry 3) and DBU (entry 4) gave similar results, suggesting that the most available and inexpensive TEA should be considered as the base of choice. Next, we conducted numerous reactions to optimize the reaction solvent. The results obtained (entries 5-13) were somehow unexpected. For example, in the cases of using toluene (entry 7) and MeOH (entry 10) as the solvent, the additions did not take place at all. Another important trend we found was that polar solvents (entries 5, 6, 8 and 9) are detrimental for the stereochemical outcome. Quite interesting, we also found that application of Et_2O (entry 12) and dioxane (entry 13) as the solvents gave dramatically different results, as compared to that of THF. On the other hand, analog of THF, 2-Me-THF, gave most promising result (entry 11). Further optimization of the reaction conditions by changing such parameters as concentration (entries 14-18) and temperature

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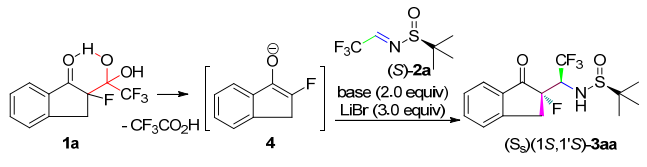
(entries 19-23) allowed us to determine the most favorable condition (entry 20). It is interesting to note that lowering the reaction temperature had almost no effect on the reaction rate, as even at -60 °C (entry 21) the addition reaction was completed within 5 minutes furnishing the target product with excellent diastereoselectivity and yield.

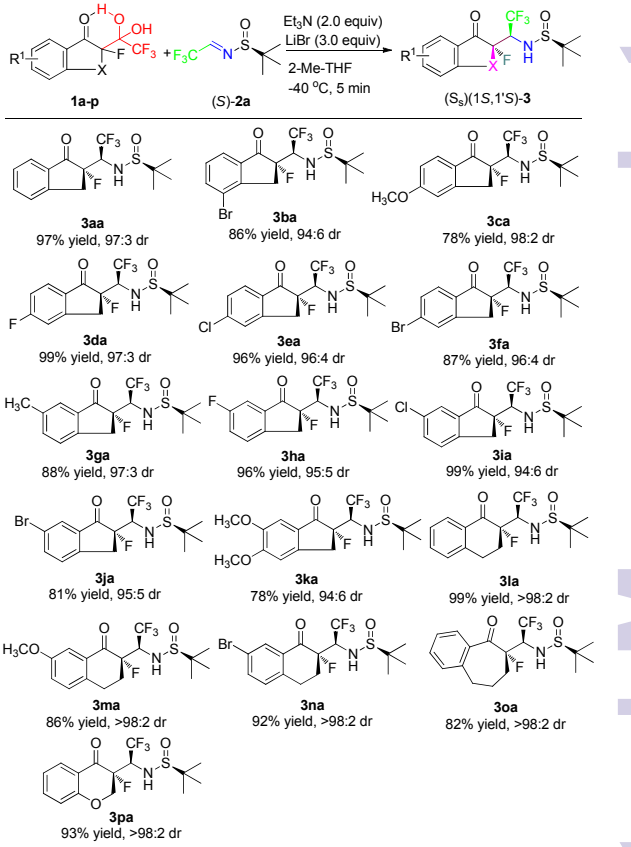
Table 1 Optimization of the reaction conditions for the detrifluoroacetylative Mannich addition reaction of keto-hydrate **1a** and imine (*S*)-**2a**[a]



Entry	Base	Solvent (mL)	Temp (°C)	Time (min)	Yield (%)[b]	Dr[c]
1	Et_3N	THF (2)	20	3	95	92:8
2	DABCO	THF (2)	20	3	93	92:8
3	DIPEA	THF (2)	20	5	92	92:8
4	DBU	THF (2)	20	10	81	90:10
5	Et_3N	DMF (2)	20	3	34	95:5
6	Et_3N	CH_3CN (2)	20	3	75	76:24
7	Et_3N	Toluene (2)	20	10	0	-
8	Et_3N	CH_2Cl_2 (2)	20	3	37	61:39
9	Et_3N	$CHCl_3$ (2)	20	3	18	53:47
10	Et_3N	CH_3OH (2)	20	10	0	-
11	Et_3N	2-Me-THF (2)	20	3	93	93:7
12	Et_3N	Et_2O (2)	20	3	82	79:21
13	Et_3N	Dioxane (2)	20	3	85	86:14
14	Et_3N	THF (10)	20	3	95	93:7
15	Et_3N	DMF (10)	20	3	32	94:6
16	Et_3N	2-Me-THF (10)	20	3	94	95:5
17	Et_3N	Et_2O (10)	20	3	81	84:16
18	Et_3N	Dioxane (10)	20	3	86	87:13
19	Et_3N	2-Me-THF (10)	0	5	95	96:4
20	Et_3N	2-Me-THF (10)	-40	5	97	97:3
21	Et_3N	2-Me-THF (10)	-60	5	96	97:3
22	Et_3N	2-Me-THF (10)	-78	10	72	97:3
23	Et_3N	2-Me-THF (10)	-95	10	41	97:3

[a] Reaction condition: di-ketone hydrates **1a** (0.2 mmol), CF_3-sulfinylimine **2a** (0.24 mmol), LiBr (0.6 mmol), base (0.4 mmol). [b] Isolated yield. [c] Determined by ^{19}F NMR.

Our next research goal was the examination of substrate scope for this detrifluoroacetylative Mannich addition reaction. First, we investigated the reactions of various keto-hydrates **1a-p** with imine **2a** (Scheme 2). As shown in Scheme 2, in the 2,3-dihydroinden-1-one series, the presence of a substituent on the phenyl ring of starting **1a-p** had almost no effect on chemical yields as well as the diastereoselectivities. For example, products **3** containing electron withdrawing (**3ba**, **3da**, **3ea**, **3fa**, **3ha**, **3ia**, **3ja**) or electron donating (**3ca**, **3ga**) groups, including di-substituted **3ka**, were isolated in good to excellent yields (78-99%) and diastereoselectivities (dr > 95:5). Very interestingly, in the 3,4-dihydronaphthalen-1-one series, clearly better diastereoselectivity was observed. And products **3la**, **3ma** and **3na** were isolated as pure diastereomers in excellent chemical yields (99%, 86% and 92% respectively). The same complete stereocontrol was observed in the case of 6,7,8,9-tetrahydrobenzo[7]annulen-5-one derived product **3oa**, albeit isolated with a bit lower chemical yield (82%). Finally, the reaction of keto-hydrate **1p** with imine **2a** was nearly perfect giving rise to 2,3-dihydrochromen-4-one containing product **3pa** in 93% yield and complete diastereoselectivity.



Scheme 2 Substrate generality study of the detrifluoroacetylative Mannich addition reactions of imine (*S*)-**2a** with keto-hydrates **1a-p**.

In the second part of the substrate scope study for this detrifluoroacetylative Mannich addition reaction, we were interested to know the effect of various fluoro-alkyl substituents, bulkier than CF_3 group, on starting imines **2** for the stereocontrol of the reactions. The results were presented in Scheme 3. We found that imines **2b** and **2c**, containing CF_2Cl and CF_2Br groups respectively, reacted well with dihydroinden-1-one derived keto-hydrate **1a** furnishing products **3ab** and **3ac** with excellent yields and diastereoselectivities. Even better results were obtained in the reactions of imines **2b**,**c** with keto-hydrate **1l** containing 2,3-dihydrochromen-4-one frame. In all reactions of **1l** with imines **2b-f** containing CF_2Cl, CF_2Br, C_2F_5, C_3F_7 and C_4F_9 groups, only single diastereomeric products **3lb-f** were detected in the reaction mixtures. Lower chemical yield in the case of imine **2f**, bearing C_4F_9 substituent can be explained by some fluorous properties of product severely complicating its isolation and purification. Similarly excellent stereochemical outcome was registered for the reactions of 2,3-dihydrochromen-4-one derived keto-hydrates **1p** with imines **2b-d** bearing CF_2Cl, CF_2Br and C_2F_5 groups, allowing preparation of diastereomerically pure products **3pb**, **3pc** and **3pd** in high yields without any need in additional purification. Finally, seven-membered ring containing keto-hydrate **1o** cleanly reacted with imine **2b** bearing a CF_2Cl group providing the target product **3ob** with high yield and diastereomeric purity. The configuration of all products **3** was assigned as (S_s)(1*S*)(1'*S*) according to the single crystal X-ray analysis of **3ka** (see SI).

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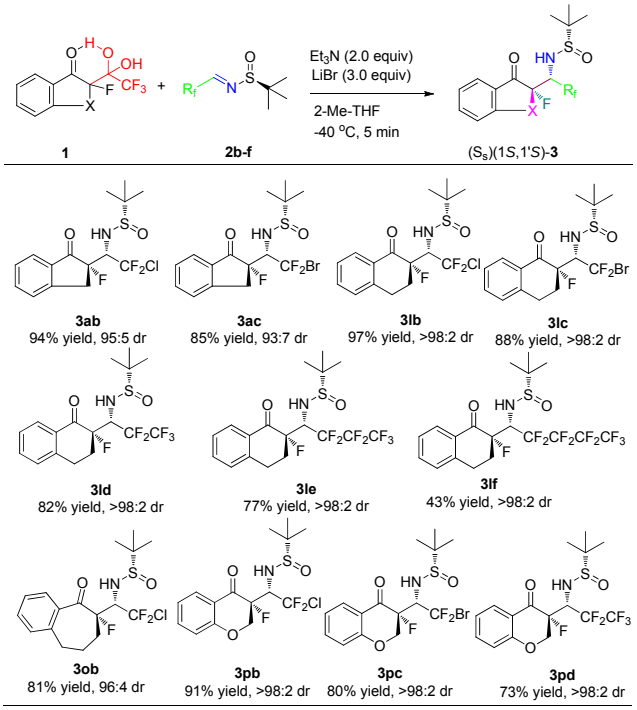


Scheme 3 Substrate generality study of the detrifluoroacetylative Mannich addition reactions of imines (*S*)-**2b-f** with keto-hydrates **1**.

Knowing the absolute configuration of the reaction products, we next suggested a plausible reaction mechanism to account for the observed stereochemical preferences in this detrifluoroacetylative Mannich addition reaction. In our previous research on the addition reactions of imine **2a**, it was established that imine **2a** reacts in the s-*cis* conformation leading to (*S*) configuration of the newly created C-CF_3 stereogenic center in the corresponding addition products.[20] Accordingly, we can propose three transition states **A**-**B** (TSs) (Figure 1) to account for the (S_s)(1*S*)(1'*S*) absolute configuration of the major products **3**. Considering TSs **A**-**C**, one may agree that in the TSs **A** and **C** the molecules of enolate and imine are overlapping suggesting some repulsive steric interactions. For instance, in TS **A** the sulfinimine moiety is over the phenyl ring and in TS **C** the stereocontrolling CF_3 group[21] is in sterically unfavorable position. In sharp contrast, in TS **B** there are no any obvious steric conflicts as the sulfinimine and trifluoromethyl groups are away from the enolate bicyclic frame. Moreover, TS **B** is chair-like and therefore might be the most stereochemically accessible. Furthermore, TS **B** allows for minimum charge separation,[22] from the enolate oxygen to the imine nitrogen, within the same chelated structure. Most importantly, TS **B** can explain the remarkable structural generality observed in these reactions. Thus, the enolate phenyl ring is totally free of any steric interactions and therefore can allow for the presence of virtually any substituent. Similarly, the CF_3 group is pointed away from the enolate molecule and in this position can accommodate any bulkier group than the trifluoromethyl, such as CF_2Br or long C_4F_9 substituents. Consequently, TS **B** provides quite reasonable and resounding explanation for the observed very high diastereoselectivity and structural generality.

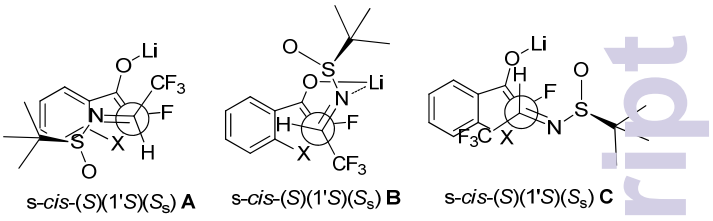
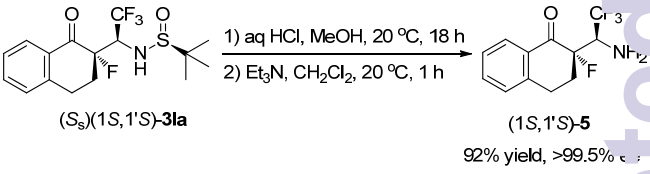


Figure 1 Possible TS **A**-**C** in the reactions of keto/hydrates **1** with imine **2a**.

As the final synthetic effort in this study we decided to demonstrate deprotection of products **3** and isolation of free amino compounds. To this end we selected product **3la** (Scheme 4) and subjected it to typical acidic hydrolysis followed by treatment with TEA.[23] Compound **5**, possessing free amino group was isolated in 92% yield. Considering relatively high C-H acidity of the C-CF_3 stereogenic center[24] we were a bit concerned about possible racemization during the deprotection procedure. Therefore, we conducted detailed HPLC study (see SI) and confirmed enantiomeric integrity (>99.5% ee) of amine **5**. This result discloses that there is no racemization during deprotection process.



Scheme 4 Deprotection of product **3la** and isolation of free amine **5**.

Conclusions

In summary, a practical method for asymmetric synthesis of quaternary C-F α-fluoro-β-keto-amino compounds has been explored, which was predicated on the idea of detrifluoroacetylative Mannich addition reactions between 2-fluoro-1,3-di-ketones/hydrates and chiral *N*-sulfinyl-imines via C-C bond cleavage. The operational ease of these transformations coupled with excellent yields, stereochemical outcome and broad structural generality bodes well for its widespread application for practical preparation of α-fluoro-β-keto-amino compounds.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedures, full spectroscopic data for compounds **3**, **5** and copies of ^{1}H NMR and ^{13}C NMR spectra]. See DOI: 10.1039/b000000x/

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