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Lewis acid-catalyzed regioselective synthesis of chiral α-fluoroalkyl amines *via* asymmetric addition of silyl dienolates to fluorinated sulfinylimines†

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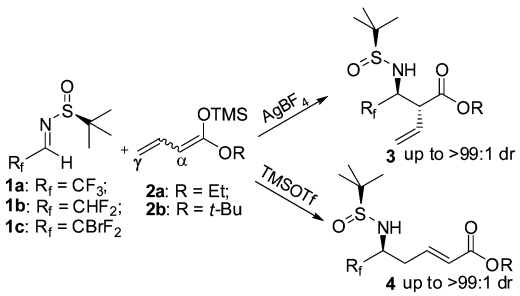
A tunable and highly regio- and diastereoselective addition of acyclic silyl dienolates 2 to several α-fluoroalkyl sulfinylimines 1 was developed. By appropriate choice of the Lewis acid catalyst, two new chiral α-fluoroalkyl amines 3 and 4 were obtained in good yields and excellent diastereoselectivities (up to >99 : 1 dr), respectively.

Over the last decades, fluorinated compounds have attracted considerable attention for use in agrochemicals, pharmaceuticals, and materials.[1] Of particular interest are fluorine-containing biologically relevant amino derivatives. α-Fluoroalkyl amines (R_fCHRNH_2) have become important building blocks for the preparation of fluorinated biologically active compounds.[2] Asymmetric synthesis of chiral α-fluoroalkyl amines is a significant task of organic synthesis, and a variety of methodologies have been developed. There are three major approaches to synthesize chiral α-fluoroalkyl amines, as follows: (a) asymmetric reduction of fluorinated ketimines,[3] (b) asymmetric fluoroalkylation of aldimines,[4] and (c) asymmetric addition to fluorinated aldimines.[5] The last method is most widely used, and takes advantage of the easy preparation of fluorinated substrates and the diversity of addition reactions. In 2007, Truong and co-workers reported the first asymmetric addition of (S_S)-*N*-*tert*-butanesulfinyl (3,3,3)-trifluoroacetaldimine **1a** with various aryllithium reagents, giving the corresponding products in good to excellent diastereoselectivities.[6] After that, compound **1a** has become an important multifunctional chiral synthon, which has been widely used in the preparation of a great variety of organic compounds containing the chiral α-trifluoromethyl amino moiety.[5c–e,g,7] Encouraged by these results, we were interested in the development of similar synthons **1b** and **1c** containing other important fluoroalkyl groups, difluoromethyl group (CHF_2)[8] and bromodifluoromethyl group ($CBrF_2$).[9] Meanwhile, most of the reported addition reactions to compound **1a** were performed under basic conditions. It is highly desirable to develop new variations of asymmetric addition reactions under neutral or acidic conditions. In continuation of our research on fluorinated chiral amines,[10] we disclose here the first Lewis acid-catalyzed regio- and diastereoselective addition of acyclic silyl dienolates **2** to several α-fluoroalkyl sulfinylimines **1** (Scheme 1). In the presence of $AgBF_4$ (0.1 eq.), the Mannich type reaction happened to give the α-addition products chiral β-fluoroalkyl-β-amino-α-vinyl esters **3** in good yields and excellent diastereoselectivities (up to >99 : 1 dr). When TMSOTf (1.0 eq.) was used as a Lewis acid, sulfinylimines **1** underwent vinylogous Mannich reaction to afford the γ-addition products chiral δ-fluoroalkyl-δ-amino-α,β-unsaturated esters **4** also in good yields and excellent diastereoselectivities (up to >99 : 1 dr). It was noteworthy that this tunable regioselectivity addition has been rarely reported,[11] as exclusive γ-selectivity has always been observed in acid-catalyzed addition reaction of silyl dienolate.[12] To the best of our knowledge, no work has been reported on the synthesis of these chiral fluorinated polyfunctional amines **3** and **4** before, which are interesting building blocks for the synthesis of novel fluorinated biologically active compounds.



Scheme 1 Lewis acid catalyzed regio- and diastereoselective synthesis of chiral α-fluoroalkyl amino units.

Sulfinylimine **1a** and dienolate **2a** were initially chosen as the test substrates to explore the addition reaction. According to previous work, two Lewis acid catalysts AgOTf[11] and $Sc(OTf)_3$ (ref. 13) were employed in the reaction (Table 1, entries 1 and 2). AgOTf catalyzed the reaction quite well, while $Sc(OTf)_3$ resulted in a complex reaction. Other Ag(I) salts, $AgClO_4$ and $AgBF_4$, were also investigated

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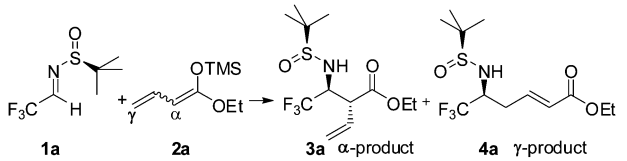
Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	Yield **3a** + **4a**[b] (%)	**3a** : **4a**[b]	**3a**[b] (dr)	**4a**[b] (dr)
1	AgOTf	THF	99	2.1 : 1	87 : 13	90 : 10
2	$Sc(OTf)_3$	THF	Complex	—	—	—
3	$AgBF_4$	THF	99	1.7 : 1	92 : 8	98 : 2
4	$AgClO_4$	THF	98	1.9 : 1	88 : 12	75 : 25
5	$AgBF_4$	*t*-BuOMe	96	1.1 : 1	87 : 13	99 : 1
6	$AgBF_4$	Toluene	95	1.0 : 1	88 : 12	86 : 14
7	$AgBF_4$	CH_2Cl_2	99	3.7 : 1	93 : 7	85 : 15
8[c]	$AgBF_4$	CH_2Cl_2	99	4.9 : 1	95 : 5	84 : 16
9[d]	$AgBF_4$	CH_2Cl_2	99	6.0 : 1	96 : 4	86 : 14
10[e]	$AgBF_4$	CH_2Cl_2	96	4.5 : 1	94 : 6	86 : 14
11[f]	TMSOTf	CH_2Cl_2	98	1 : 39	63 : 37	97 : 3

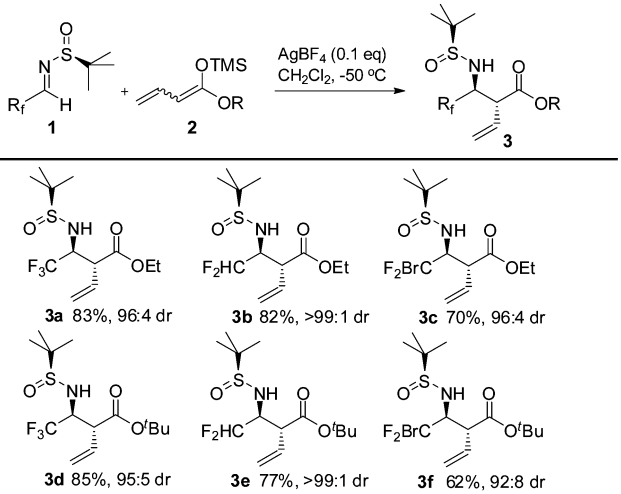
[a] The reaction was performed with **1a**/**2a** = 1 : 1.2, catalyst (0.1 eq.), solvent (2.0 mL), under nitrogen, at 0 °C (0.5 mmol scale). [b] Ratios and yields were determined by ^{19}F NMR spectroscopy of the crude reaction mixture using benzotrifluoride as an internal standard. [c] −30 °C. [d] −50 °C. [e] −78 °C. [f] TMSOTf (1.0 eq.), −78 °C.

in the reaction (entries 3 and 4). Among these three Ag(I) catalysts, $AgBF_4$ was proven to be the best one. To further improve the regioselectivity of the addition reaction, different solvents were evaluated (entries 5–7). The regioselectivity was increased to 3.7 : 1 together with slightly improved diastereoselectivity of **3a** when the reaction was performed in CH_2Cl_2 (entry 7). The reaction temperature also played an important role (entries 8–10). The regioselectivity was increased to 6.0 : 1 and the diastereoselectivity of **3a** was also slightly improved when the reaction was carried out at −50 °C (entry 9). In the process of optimizing the reaction conditions for generating product **3a**, the product **4a** was formed no matter how the reaction conditions were changed. We concluded that the divorced TMS^+ form silyl dienolates **2a** may also catalyzed this reaction to generate **4a**.[14] Therefore, TMSOTf (1.0 eq.) was chosen as the catalyst. To our delight, compound **4a** was formed in high yield with excellent regioselectivity and diastereoselectivity (entry 11). Finally it was found that with an appropriate Lewis acid, the α-product (by $AgBF_4$) or γ-product (by TMSOTf) could be selectively formed.

Under the optimum reaction conditions, the scope of substrates of $AgBF_4$ catalyzed Mannich-type addition reaction was explored (Table 2). Different α-fluoroalkyl sulfinylimines **1** and acyclic silyl dienolates **2** reacted to give the corresponding product **3** in good yields and excellent diastereoselectivities. Especially for sulfinylimine **1b**, β-difluoromethyl-β-amino-α-vinyl esters **3b** and **3e** were both formed with extremely high diastereoselectivities (>99 : 1). High reaction yields and excellent diastereoselectivities were also observed in the TMSOTf catalyzed vinylogous Mannich reaction of different α-fluoroalkyl sulfinylimines **1** and acyclic silyl dienolates **2** (Table 3). It was noteworthy that this procedure was also applicable to cyclic diene **2**, which was converted to the corresponding products **4e–g** in excellent yields and diastereoselectivities.

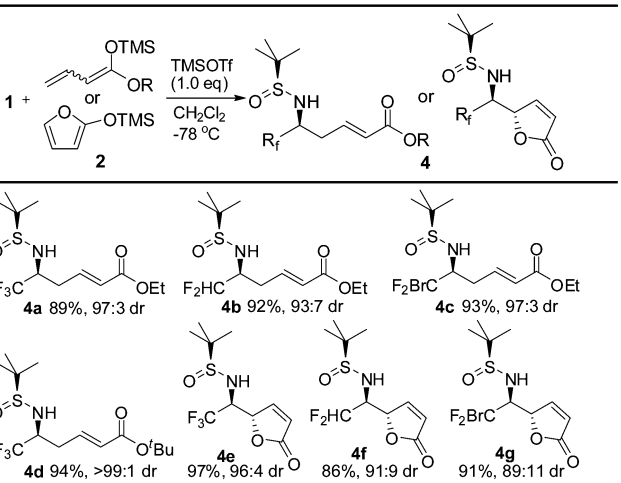
The absolute configuration of products **3** and **4** was confirmed by X-ray crystallographic analysis of compounds **3b**, **3d** and **4e** (see

Table 2 Synthesis of chiral β-fluoroalkyl-β-amino-α-vinyl esters **3** in the $AgBF_4$ catalyzed Mannich-type addition reaction[a,b]



[a] All reaction yields are isolated yields. [b] Dr values are determined by ^{19}F NMR spectroscopy of the crude reaction mixture.

Table 3 Synthesis of chiral δ-fluoroalkyl-δ-amino-α,β-unsaturated esters **4** in the TMSOTf catalyzed vinylogous Mannich reaction[a,b]



[a] All reaction yields are isolated yields. [b] Dr values are determined by ^{19}F NMR spectroscopy of the crude reaction mixture.

ESI†). The high regio- and diastereoselectivities of different Lewis acid-catalyzed reactions may be explained by different transition states (Fig. 1). In the case of the TMSOTf catalyzed reaction, the γ-selectivity is a rational outcome of the normal pathway of acid-catalyzed addition reaction of silyl dienolate.[12] The *S*-configuration of the newly formed chiral carbon center in products **4** could be explained by the non-chelated transition state model TS **A**, in which the sulfinyl oxygen coordinates to TMS^+ and sterically shields the *Re* face of the imine to give the Cram product.[14b,15] When $AgBF_4$ was used as the catalyst, a chelated transition state model TS **B** was proposed. Ag^+ can coordinate to the sulfinyl oxygen atom, the sulfinyl nitrogen atom and the oxygen atom of silyl dienolate at the same time,[11] which leads to *Re*-attack to give α-addition products **3** with (S_S, C_S, C_R)-configurations.

The *N-tert*-butylsulfinyl group can serve as not only an efficient chiral auxiliary, but also an amine protecting group.[16]

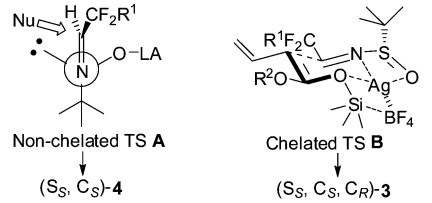
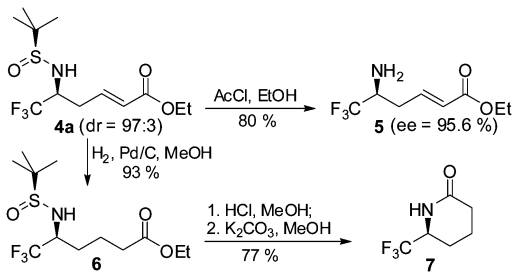


Fig. 1 Proposed transition states **A** and **B**.



Scheme 2 Further transformations of compound **4a**.

It can be readily cleaved under mild acidic conditions (Scheme 2). After deprotection, the free amine **5** was obtained in high yield without any erosion of enantiomeric purity. This result is consistent with previous reports that the sulfinamide auxiliary cleavage usually occurs without any erosion of chirality.[17] It should be noted that compound **4a** can be easily transformed to an unknown chiral trifluoromethylated piperidone **7** in high yield after hydrogenation, deprotection and subsequent cyclization.

The first Lewis acid-catalyzed asymmetric addition of silyl dienolates **2** to α-fluoroalkyl sulfinylimines **1** was developed. With an appropriate Lewis acid, the α-addtion product (by $AgBF_4$) or the γ-addition product (by TMSOTf) can be obtained in good yields and excellent diastereoselectives, respectively. These adducts are versatile synthetic intermediates and can be transformed into other chiral fluorinated amine derivatives.

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