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Highly Enantioselective Construction of Fluoroalkylated Quaternary Stereocenters via Organocatalytic Dehydrated Mannich Reaction of Unprotected Hemiaminals with Ketones

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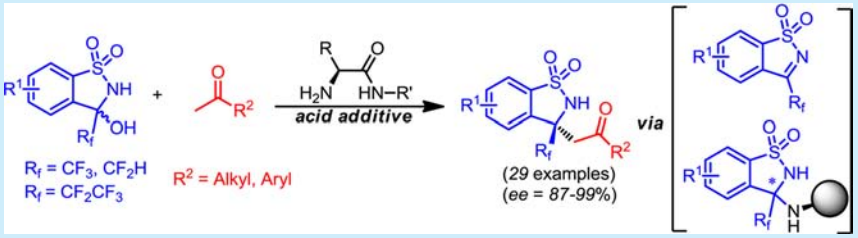
Supporting Information



ABSTRACT: A general organocatalytic asymmetric dehydrated Mannich reaction of fluoroalkyl hemiaminals with ketones is reported. In this Mannich reaction, previously less explored aryl ketones showed great reactivity. By virtue of this efficient method, a wide range of biologically active β-amino ketones were directly obtained. More importantly, two different intermediates involved in the reaction were detected and identified by ^{19}F NMR and HRMS analysis. Furthermore, the synthetic utility of the products was demonstrated by the synthesis of the biologically active fluoroalkyl β-amino alcohols.

In recent decades, the synthesis of chiral fluoroalkylated compounds has been the subject of intense interest, primarily because of the unique role of the fluoroalkyl group in the enhancement of pharmacological and agrochemical activities (Figure 1).[1,2] Among these fluoroalkylated compounds, the fluoroalkyl β-aminoalcohols as a privileged structural motif are widely found in β-secretase inhibitors, which are potent drugs used in the Alzheimer's disease.[3] Despite the great synthetic utility of this structure, there remains a formidable challenge in accessing a broad range of fluoroalkyl β-aminoalcohols with an asymmetric catalytic method.[4,3c] In this context, we synthesized a novel fluoroalkylated hemiaminal **1** from sulfamide derivatives and successfully employed it in a dehydrated Mannich reaction.[5] This reaction provided a reliable and scalable access to a broad spectrum of biologically active fluoroalkyl β-amino alcohols by a facile derivatization (Figure 1).

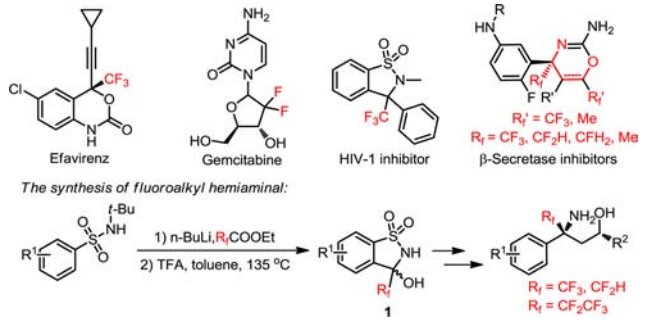


Figure 1. Selected pharmaceutically active molecules containing fluoroalkyl groups and the synthesis of fluoroalkylated hemiaminal **1**.

Hemiaminals as important intermediates in the formation of imine and iminium are widely found in the enzyme-catalyzed Mannich reaction.[6] Inspired by this enzymatic Mannich reaction, hemiaminals as an electrophile have been extensively explored in asymmetric transformation especially since the pioneering work of Jacobsen (Scheme 1).[7] However, a remarkable breakthrough in the Mannich-type reaction of hemiaminals with carbonyl compounds has only recently been achieved by Kanai and Koley groups (Scheme 1).[7g,i] Nevertheless, unprotected hemiaminals, representing a more challenging class of substrate in the dehydrated Mannich reaction, have received far less attention due to their inherent instability. Consequently, we first described a general enantioselective dehydrated Mannich reaction of unprotected hemiaminals herein by using a simple chiral amino acid amide catalyst. In this process, fluoroalkylated quaternary stereocenters were readily achieved with an unprecedented substrate scope. We found that not only alkyl but also aryl ketones, which were notoriously low reactive substrates in organocatalytic reactions,[8] could be applied to provide the corresponding products with excellent enantioselectivities.

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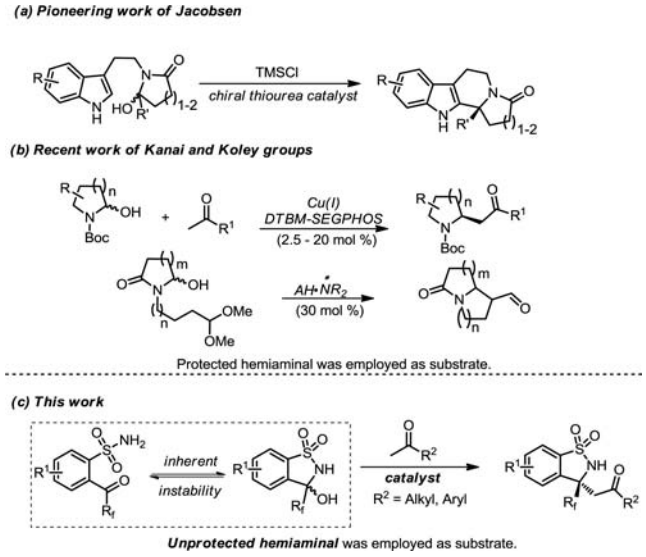
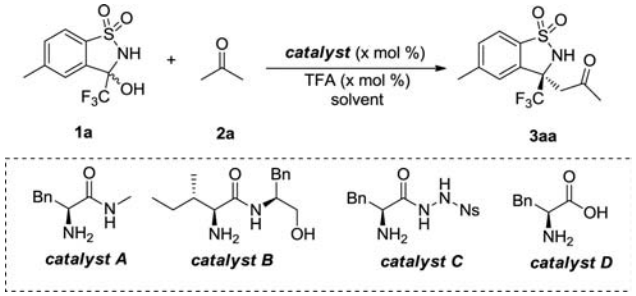
Scheme 1. Asymmetric Dehydrated Mannich Reaction of Hemiaminals with Carbonyl Compounds



Initially, we embarked on this dehydrated Mannich reaction with our previously developed catalyst amino sulfono-hydrazide (**catalyst C**) with a 20 mol % catalyst loading, which showed great activity in the direct Mannich reaction of cyclic ketimines.[8e] Unfortunately, only a trace of product was detected after a long reaction time (Table 1, entry 1). Considering the poor performance of this double hydrogen bonding catalyst, we assumed that amino acid amide **catalyst A** with a less sterically hindered hydrogen bond donor might accelerate this dehydrated Mannich reaction. As expected, a preliminary enantioselectivity was obtained with moderate yield (Table 1, entry 3). Replacing TFA with a weakly acidic benzoic acid allowed a significant improvement in the yield of this reaction (Table 1, entries 5−6). Various solvents were also examined, and chloroform proved to be optimal (Table 1, entries 3−5). Pleasingly, reduction of the catalyst loading to 5 mol % still maintained excellent enantioselectivity and yield when the dehydrated Mannich reaction was scaled up to 0.3 mmol (Table 1, entry 7). Moreover, comparable performance was observed when **catalyst B** was employed, which contains multiple sites for hydrogen bonding (Table 1, entry 8). After optimization, the best enantioselectivity as well as yield was obtained when the reaction was carried out in the presence of **catalyst A**/**catalyst B** and 2,6-difluorobenzoic acid as an additive in chloroform at room temperature (Table 1, entries 7−8).

With optimized conditions in hand, we investigated the generality of the dehydrated Mannich reaction with various sulfamide-derived hemiaminals. As seen in Table 2, the reaction was tolerant of electronically and sterically diverse substituents on the hemiaminals **1** (Table 2, entries 1−12). Specifically, the sterically congested substrate **1l** proceeded smoothly in this efficient transformation, thereby giving access to the product with excellent enantioselectivity, albeit with a slight erosion of yield (Table 2, entry 12). The exchange of the trifluoromethyl group for difluoromethyl and perfluoroethyl groups in substrate **1** led to almost no change in terms of yield and *ee* value (Table 2, entries 13−14).

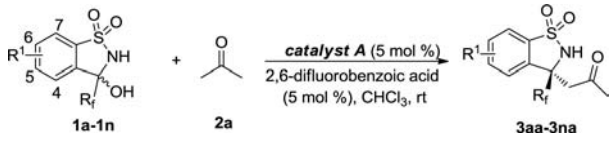
Table 1. Optimization of the Enantioselective Dehydrated Mannich Reaction of Fluoroalkylated Hemiaminals with Acetone[a]



entry	catalyst	solvent	*x*	yield (%)[b]	*ee* (%)[c]
1[d]	**catalyst C**	toluene	20	trace	n.d.
2[d]	**catalyst D**	toluene	20	trace	n.d.
3	**catalyst A**	toluene	20	72	89
4	**catalyst A**	EtOAc	20	66	77
5[e]	**catalyst A**	$CHCl_3$	20	74(81)	92(93)
6[f]	**catalyst A**	$CHCl_3$	20	97	97
7[g]	**catalyst A**	$CHCl_3$	5	96	97
8[g]	**catalyst B**	$CHCl_3$	10	93	97

[a]The reaction of **1a** (0.1 mmol) with **2a** (0.5 mmol) was performed in the presence of **catalyst** (*x* mol %) and TFA (*x* mol %) in solvent (0.5 mL) at room temperature for 24 h. [b]Yield of isolated product. [c]The *ee* value of the product **3aa** was determined by HPLC on a chiral stationary phase. [d]The reaction was performed for 72 h. [e]The data in the parentheses were observed when the reaction was performed in the absence of TFA. [f]2,6-Difluorobenzoic acid (20 mol %) was used in place of TFA. [g]The reaction was performed on the 0.3 mmol scale under standard conditions.

Table 2. Scope of Hemiaminals 1 in the Enantioselective Dehydrated Mannich Reaction[a]



entry	3	R^1	R_f	yield (%)[b]	*ee* (%)[c]
1	**3aa**	5-Me	CF_3	96	97
2	**3ba**	–	CF_3	90	96
3	**3ca**	5-*t*Bu	CF_3	98	94
4	**3da**	5-OMe	CF_3	90	96
5[d]	**3ea**	5-OCF_3	CF_3	97	92
6	**3fa**	5-Cl	CF_3	95	91
7	**3ga**	5-F	CF_3	96	93
8[e]	**3ha**	5,6-$(CH)_4$	CF_3	87	97
9	**3ia**	6-Me	CF_3	99	97
10	**3ja**	7-Cl	CF_3	96	92
11[e]	**3ka**	4-F	CF_3	96	92
12[e]	**3la**	4,7-$(OMe)_2$	CF_3	88	99
13	**3ma**	5-Me	CF_2H	99	97
14[e]	**3na**	5-Me	C_2F_5	99	95

[a]The reaction of **1** (0.3 mmol) with **2a** (1.8 mmol) was performed in the presence of **catalyst A** (5 mol %) and 2,6-difluorobenzoic acid (5 mol %) in $CHCl_3$ (1.5 mL) at room temperature for 36 h. [b]Yield of isolated product. [c]The *ee* value of the product **3** was determined by HPLC on a chiral stationary phase. [d]The reaction was performed for 48 h. [e]The reaction was performed in the presence of 10 mol % **catalyst B** (see details in p S5 of Supporting Information).

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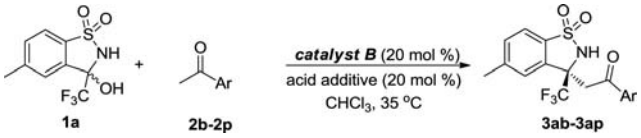
Having surveyed the scope of cyclic hemiaminals in this asymmetric dehydrated Mannich reaction, we were poised to apply this catalytic system to less studied acetophenones. To temper the lower nucleophilicity of these substrates, **catalyst B** containing a more flexible backbone was utilized with a higher catalyst loading (20 mol %). With this modified condition, we were pleased to find that a wide variety of acetophenones were compatible with this protocol and a high level of stereoselectivity was maintained (Table 3). In the cases of electron-rich substrates, which have a higher activation barrier, a satisfactory result could still be obtained by simply increasing the reaction temperature to 40 °C (Table 3, entries 7, 15). Moreover, it should be noted that multiply substituted acetophenones marginally affected the stereocontrol in this procedure (Table 3, entries 13−14).

Table 3. Scope of Acetophenones 2 in the Enantioselective Dehydrated Mannich Reaction[a]



entry	3	Ar	yield (%)[b]	*ee* (%)[c]
1[d]	**3ab**	Ph	84(85)	91(86)
2	**3ac**	4-FC_6H_4	80	91
3	**3ad**	4-ClC_6H_4	90	92
4	**3ae**	4-BrC_6H_4	92	93
5	**3af**	4-$NO_2C_6H_4$	88	91
6	**3ag**	4-$CF_3C_6H_4$	90	87
7[e]	**3ah**	4-$OMeC_6H_4$	92	92
8	**3ai**	4-PhC_6H_4	91	91
9	**3aj**	4-*t*BuC_6H_4	85	90
10	**3ak**	4-MeC_6H_4	94	91
11	**3al**	2-naphthyl	96	90
12	**3am**	3-$OMeC_6H_4$	97	90
13	**3an**	3,4-$(OCH_2O)C_6H_3$	70	88
14	**3ao**	3,4-$F_2C_6H_3$	79	89
15[e]	**3ap**	2-thienyl	74	91

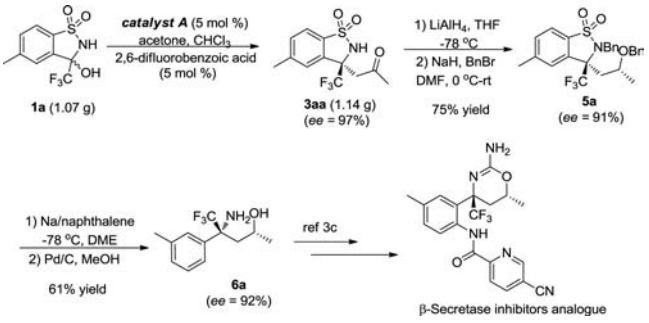
[a]The reaction of **1a** (0.3 mmol) with **2** (1.5 mmol) was performed in the presence of **catalyst B** (20 mol %) and 2,6-difluorobenzoic acid (20 mol %) in $CHCl_3$ (1.8 mL) at 35 °C for 60 h. [b]Yield of isolated product. [c]The *ee* value of the product **3** was determined by HPLC on a chiral stationary phase. [d]The data in the parentheses were observed when 20 mol % **catalyst A** was used in the place of **catalyst B**. [e]The reaction was performed at 40 °C for 60 h (see details on p S5 of Supporting Information).

To demonstrate the robust nature and operational simplicity of this dehydrated Mannich reaction, a gram-scale organocatalytic Mannich reaction was performed in the presence of 5 mol % **catalyst A** and the product **3aa** was afforded in 93% yield with an enantiomeric excess of 97% (Scheme 2). With this enantiomerically enriched *β*-amino ketone **3aa**, the corresponding *β*-amino alcohol **6a** was obtained with 92% *ee* by a four-step sequence of facile reduction, *N*-benzyl protection, sultam ring cleavage, and then deprotection. The fluoroalkyl *β*-amino alcohol structure has already been transformed into a *β*-secretase inhibitor, and our sequence therefore constitutes a formal synthesis.[3c]

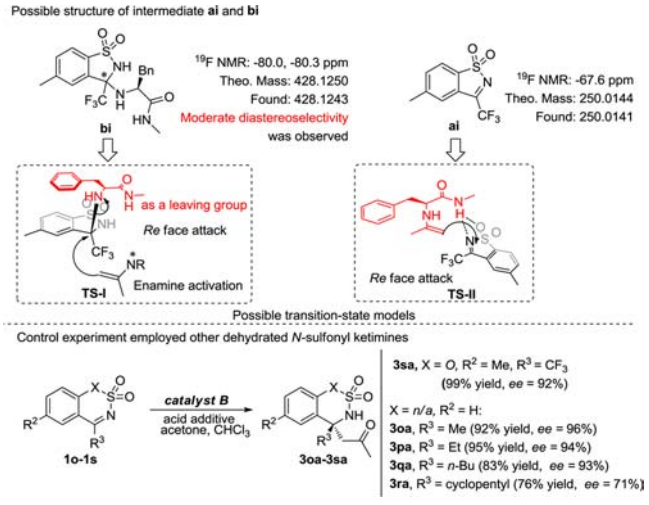
In an attempt to better understand this reaction, a ^{19}F NMR experiment was undertaken to monitor this progress.[9] Two intermediates **ai** and **bi** involved in the dehydrated Mannich reaction with chemical shifts of −67.6 and −80 ppm respectively were detected (Scheme 3). According to the further HRMS study and earlier precedent, the structures of intermediates **ai** and **bi** were identified (Scheme 3).[10,11] The corresponding possible transition-state models **TS-I**, **TS-II** were proposed on the basis of these findings and the absolute configuration of **3aa**,[12] as shown in Scheme 3. Given the presence of *in situ* generated ketimine **ai** in the reaction, the dehydrated ketimine **1s**, which had an almost identical lower-field resonance (−66.9 ppm) to intermediate **ai**, was attempted under the optimized condition and the product was afforded with 92% *ee* and 99% yield (Scheme 3). This finding confirmed that the *in situ* generated ketimine **ai** has participated in the dehydrated Mannich reaction. With this established result, other challenging substrates such as alkyl substituted ketimines were also explored. Remarkably, the ketimine could be substituted with various alkyl groups, including methyl, ethyl, *n*-butyl, and even cyclopentyl groups. The desired products, alkylated *β*-amino ketones (**3oa**−**3ra**), were provided with moderate to excellent *ee* values (Scheme 3). To the best of our knowledge, this is the first example of an asymmetric intermolecular Mannich reaction of alkyl substituted *N*-sulfonyl ketimines with acetone.[13,14]

In conclusion, a highly enantioselective dehydrated Mannich reaction of unprotected hemiaminal was first developed with an unprecedented substrate scope. A broad range of ketones,

Scheme 2. Preparative Scale Synthesis of 3aa and the Formal Synthesis of *β*-Secretase Inhibitor Analogue



Scheme 3. Intermediates and the Proposed Transition-State Models in the Dehydrated Mannich Reaction and the Control Experiment



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including alkyl and aryl ketones, were used to provide various β-amino ketones with high control of the stereoselectivity. Moreover, two important intermediates, **ai** and **bi**, were detected and identified in the reaction. The detailed mechanism study revealed the first intermolecular Mannich reaction of alkyl-substituted *N*-sulfonyl ketimines with acetone. In addition, this useful method offers a general access to fluoroalkyl β-amino alcohols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02514.

Typical experimental procedure and characterization for all products (PDF)

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Notes

The authors declare no competing financial interest.

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(9) (a) For details of the ^{19}F NMR study, see pp S10−S13 of the Supporting Information. (b) The reaction pathway was also studied. See details on pp S8−S9 of the Supporting Information.

(10) For details of the HRMS study see pp S15−S17 of the Supporting Information.

(11) A *N,O*-hemiacetal intermediate (similar to **bi**) was found in the aldol reaction of trifluoroacetophenone; see: Duangdee, N.; Harnying, W.; Rulli, G.; Neudörfl, J.; Gröger, H.; Berkessel, A. *J. Am. Chem. Soc.* **2012**, *134*, 11196.

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(14) For a detailed mechanism study of transition state **TS-I**, see p S14 of the Supporting Information.

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