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An aza-Michael addition protocol to fluoroalkylated β-amino acid derivatives and enantiopure trifluoromethylated N-heterocycles†

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The aza-Michael reaction with β-fluoroalkylated acrylates provided the corresponding fluoroalkylated β-amino acid derivatives in up to 99% yield under catalyst- and solvent-free conditions. An enantioenriched β-trifluoromethylated β-amino acid was obtained in good yield through a scale-up diastereoselective aza-Michael addition, which facilitated the installation of enantiopure trifluoromethylated analogues of β-lactam and dihydroquinolin-4-one.

It has been well demonstrated that the incorporation of the fluoroalkylated group can effectively enhance the lipophilicity, electronic interactions, binding selectivity and stability to metabolic degradation of the parent compounds.[1] β-Amino acids are present in naturally occurring biologically active peptides,[2] and have found a wide spectrum of applications in organic synthesis and medicinal chemistry.[3] In view of the synthetic application of fluorinated β-amino acids to fluorinated β-lactams,[4] or key motifs in peptides,[5] peptidomimetics[6] and other molecules[7] with various important biological activities (Fig. 1), the development of reliable methodologies for their preparation has been a topic of great interest in the last decade.[8] In particular, the asymmetric synthesis of optically pure β-trifluomethylated (CF_3) β-amino acids (TFAAs) displays a challenge for organic chemists. The enantioselective approach remains relatively rare and difficult to achieve high enantioselectivity.[9] An alternative strategy is based on diastereoselective transformation. All diastereoselective protocols explored so far to generate TFAAs involved reactions with trifluoromethylated ketones or imines exclusively.[10] For instance, the Fustero group described a diastereoselective addition of chiral 2-(*p*-tolylsulfinyl)-benzylic carbanions to trifluoromethylated imines followed by a desulfuration/oxidation sequence to obtain optically pure TFAA derivatives in good yields.[10b] In the meantime, Saigo *et al.* disclosed a highly practical asymmetric hydride reduction of a seven-membered cyclic enamino-ester derived from 4,4,4-trifluoro-3-oxobutanoate to form chiral TFAA.[10c] In 2013, Grellepois applied the asymmetric Reformatsky reaction with chiral α-CF_3 *N-tert*-butanesulfinyl hemiaminals to the preparation of TFAA derivatives and further incorporation into peptides.[10f] Recently, Shibata, Soloshonok and co-workers demonstrated a practical approach to enantiomerically pure TFAAs after hydrolysis and decarboxylation of the corresponding β-aminomalonates obtained from diastereoselective Mannich additions.[10g]

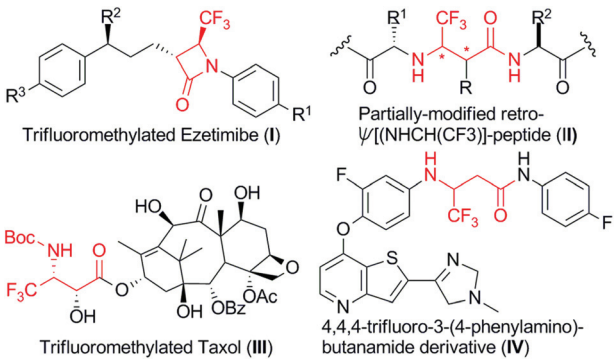

Fig. 1 Selected bioactive compounds containing fluorinated β-amino acid scaffolds.

One of the most simple and powerful tools to construct the β-amino acid skeleton is the 1,4-addition of amines to unsaturated esters (aza-Michael reaction). Over the past few decades, tremendous efforts have been devoted to the development of highly efficient and selective aza-Michael reactions.[11] These reactions are usually accomplished in an organic solvent with the assistance of an organo- or organometallic catalyst. The philosophy of green chemistry requires that all atoms are converted into the desired products by minimizing or avoiding the use of solvents, most ideally, in the absence of any catalyst. The aza-Michael addition under both catalyst- and solvent-free conditions remains a challenge, but highly desirable for the

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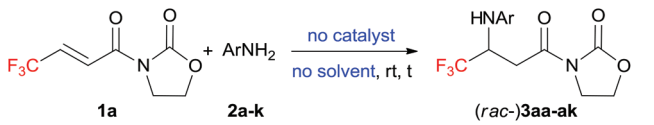
economic and environmentally benign advantage. To the best of our knowledge, there is no literature that describes the synthesis of TFAAs and their derivatives *via* aza-Michael addition without any catalyst and solvent. In this context, as continuing efforts on synthetic fluorine chemistry,[12] we report herein the research results on a simple and novel aza-Michael reaction between fluorinated acrylic acid derivatives **1** and amines **2** without any solvent and catalyst. Under the same conditions, the scale-up synthesis *via* diastereoselective aza-Michael addition allows for an efficient access to enantiopure TFAA **6**, and thus to two enantioenriched trifluoromethylated heterocyclic compounds as well (see Scheme 2).

Previously, we have shown the versatility of β-trifluoromethylated acrylate **1a** in the asymmetric Friedel–Crafts alkylation to install optically pure trifluoromethylated heliotridane.[12b] In order to explore more functions of **1a**, we initially envisioned a catalytic asymmetric aza-Michael addition between **1a** and aniline **2a** to obtain a chiral analogue of **3aa** with the β-CF_3 amino acid skeleton. However, even after a thorough screening of several parameters of the model reaction, including the 3,3′-substituents of chiral BINOL-derived phosphoric acid catalysts, organic solvents and temperature, efficient and highly enantioselective transformation to **3aa** was hardly established. A control experiment revealed that the mixture of **1a** and **2a** in the absence of any catalyst in CH_2Cl_2 at room temperature gave **3aa** in 45% yield. But the yield is difficult to be improved by prolonging the reaction time. To our delight, neat conditions enabled us to establish a novel reaction system, which afforded the desired compound **3aa** in quantitative yield after 22 h (entry 1, Table 1). Most importantly, after evaporating the very small excess of aniline, **3aa** was obtained with a satisfactory purity. **3aa** could be further purified by preparative thin layer chromatography (PTLC). It should be noted that this is the first case of aza-Michael addition reaction with the trifluoromethylated electrophile under catalyst- and solvent-free conditions. Because all acrylate substrates used herein are in the solid state, all amines selected in the aza-Michael protocol are limited to be liquid at room temperature for guaranteeing a homogeneous reaction process.

In the established reaction system, a variety of primary aromatic amines reacted efficiently with **1a** to form racemic TFAA derivatives **3** (Table 1). Methoxyl-substituted sterically hindered amine **2b** resulted in a slight drop in conversion efficiency to furnish **3ab** in 95% yield after 32 h (entry 2). To our surprise, when one more electron-donating methoxyl group was introduced at the 4-position of **2b**, compound **1a** was consumed completely within 3 h (entry 3). The examination of meta-substituents showed that the electronic effect played a key role in the reaction outcomes. Amine **2d** featuring an electron-donating group (–Me) worked well (entry 4), whereas electron-withdrawing groups (–F, –Cl, –Br) yielded the adducts **3ae–3ag** with diminished levels of efficiency (entries 5–7). Notably, the presence of a strong electron-withdrawing group like a CF_3 group was also tolerated with moderate isolated yield (entry 8). Substituting the *para*-position of aniline, regardless of the electronic and steric nature, generated the target compounds **3ai–3ak** in excellent yields within 3 h (entries 9–11).

Encouraged by these results, the scope of aliphatic amine nucleophiles was next examined. From the point of view of nucleophilicity and steric hindrance, benzylamine should have a higher activity than aniline in aza-Michael reaction. Treatment of **1a** with 1.1 equivalent of benzylamine led to **3al** in 91% yield and a small amount of an amidolysis product **3al′** (eqn (1), Scheme 1). Increasing the amount of benzylamine to 2.2 equivalents mainly gave rise to **3al′** in 93% yield after 1.5 h (eqn (2), Scheme 1). Inspired by this result, we focused on the cascade aza-Michael/amidolysis reaction between **1a** and a bis-nucleophile benzylhydrazine **2m**.[13] As expected, small-ring heterocycles pyrazolidinones **3am** and **3am′**, as core structures in many pharmacological and biological active molecules,[14] were obtained in 66% and 25% yield, respectively. The less hindered amine part of the hydrazine privileged the 1,4-addition to afford the major product **3am**. In addition, a variety of N-substituents (–Me, –Et, –Bn and –$(CH_2)_2$OH) of secondary benzylamine were also tested and the corresponding products **3an–3aq** were obtained uniformly in excellent yields within a

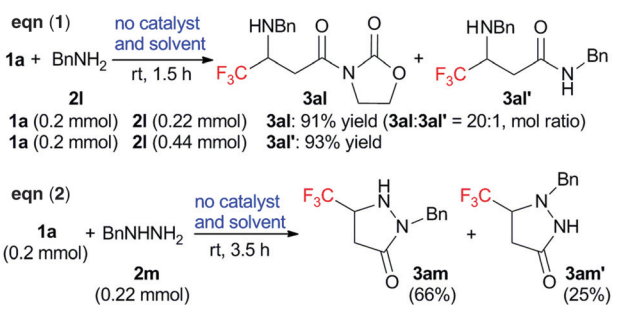
Table 1 Scope of different aromatic amine nucleophiles[a]



1a **2a-k** (*rac*-)**3aa-ak**

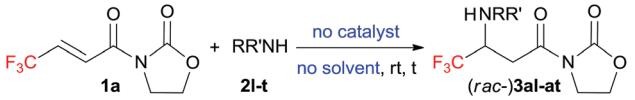
Entry	Ar	Product	Time (h)	Yield[b] (%)
1	Ph (**2a**)	**3aa**	22	97
2	*o*-OMe-Ph (**2b**)	**3ab**	32	95
3	*o*,*p*-$(OMe)_2$-Ph (**2c**)	**3ac**	3	99
4	*m*-Me-Ph (**2d**)	**3ad**	12	94
5[c]	*m*-F-Ph (**2e**)	**3ae**	60	92
6[c]	*m*-Cl-Ph (**2f**)	**3af**	56	88
7[c]	*m*-Br-Ph (**2g**)	**3ag**	36	92
8[c]	*m*-CF_3-Ph (**2h**)	**3ah**	60	52
9	*p*-Et-Ph (**2i**)	**3ai**	3	99
10	*p*-^{t}Bu-Ph (**2j**)	**3aj**	1	97
11	*p*-F-Ph (**2k**)	**3ak**	3	96

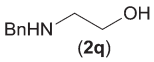
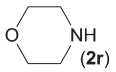
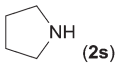
[a] All reactions were carried out using **1a** (0.2 mmol) and **2a–k** (0.22 mmol) at room temperature for the time given. [b] Isolated yield after preparative thin layer chromatography. [c] 0.30 mmol amine was used.



Scheme 1 Aza-Michael reaction between **1a** and **2l** or **2m**.

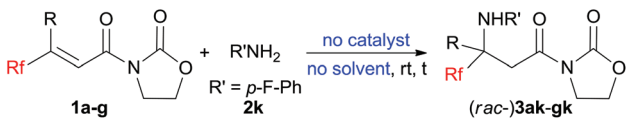
Table 2 Scope of different aliphatic amine nucleophiles[a]



Entry	RR′NH	Product	Time (h)	Yield[b] (%)
1	$BnNH_2$ (**2l**)	**3al**	1.5	91
2	Bn(Me)NH (**2n**)	**3an**	6	95
3	Bn(Et)NH (**2o**)	**3ao**	4	95
4	Bn_2NH (**2p**)	**3ap**	1.5	99
5	 (**2q**)	**3aq**	1	92
6	 (**2r**)	**3ar**	2	94
7	 (**2s**)	**3as**	2	91
8	$CyNH_2$ (**2t**)	**3at**	1.5	99

[a] All reactions were carried out using **1a** (0.2 mmol) and **2k–s** (0.22 mmol) at room temperature for the time given. [b] Isolated yield after preparative thin layer chromatography.

Table 3 Scope of various acrylate electrophiles[a]



Entry	Rf	R	Product	Time (h)	Yield[b] (%)
1	CF_3 (**1a**)	H	**3ak**	3	96
2	CF_2H (**1b**)	H	**3bk**	18	93
3	CFH_2 (**1c**)	H	**3ck**	24	92
4	CH_3 (**1d**)	H	**3dk**	44	72
5	C_2F_5 (**1e**)	H	**3ek**	18	87
6	$CClF_2$ (**11**)	H	**3fk**	6	92
7	$CBrF_2$ (**1g**)	H	**3gk**	10	87
8	CF_3 (**1h**)	Ph	**3hk**	48	0

[a] All reactions were carried out using **1** (0.2 mmol) and **2k** (0.22 mmol) at room temperature for the time given. [b] Isolated yield after preparative thin layer chromatography.

short time (entries 2–5, Table 2). In the case of two cyclic secondary amines of morpholine **2r** and pyrrolidine **2s**, comparable results were obtained (entries 6–7). Cyclohexylamine **2t** also proved to be a perfect nucleophile in this protocol (99% yield, entry 8). It should be mentioned that no cleavage of oxazolidin-2-one auxiliary through amidolysis reaction occurred under the present condition except with benzylamine **2l** and benzylhydrazine **2m**.

As evident in Table 3, we turned our attention to the scope of fluoroalkylated acrylates **1**. The electrophiles **1b–h** bearing various fluoroalkylated groups at the β-position were synthesized by using the same route as for **1a**. Modification of the

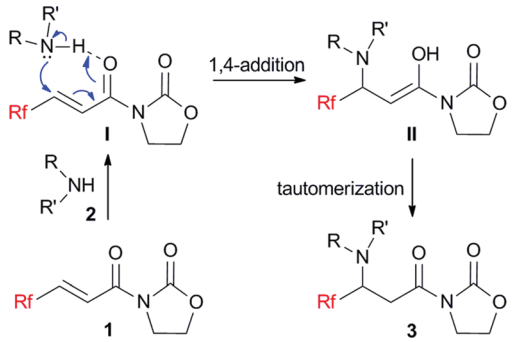
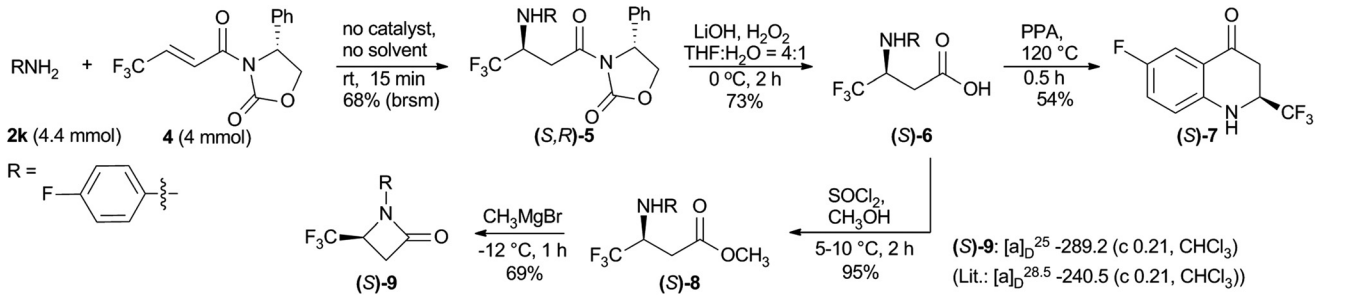


Fig. 2 Plausible mechanism of the aza-Michael reaction.

β-substituent may result in different types of β-fluoromethylated β-amino acid derivatives. The replacement of fluorine atom(s) with one or two proton(s) reduces the reaction rate (entries 2–3, Table 3). For comparison, methyl oxazolidinone **1d** was also engaged in this reaction with a markedly lower reactivity (entry 4). Other variations on the β-carbon of **1**, such as $-C_2F_5$, $-CClF_2$, and $-CBrF_2$, slightly influences the reaction speed compared with **1a** (entries 5–7). These results indicate that strong electron-withdrawing action of fluorinated groups, in particular a CF_3 group, plays a crucial role in the transformation. However, such a protocol could not be extended to β-CF_3-β-phenyl disubstituted acrylate **1h**, and no desired adduct **3hk** was delivered even after a long reaction time.

The plausible mechanism of this aza-Michael reaction is illustrated in Fig. 2. Two components of the reaction are organized through the hydrogen bonding interaction between the carbonyl oxygen atom and the amine NH proton. Sequentially, the formed intermediate **I** undergoes an intramolecular-like amine conjugate addition to provide enolized intermediate **II**. The strong electron-withdrawing nature of the CF_3 group in acrylate **1** plays a vital role in this smooth direct addition step. Finally, a rapid tautomerization occurs to generate the aza-Michael adduct **3**.

The development of novel synthetic methodologies for optically pure fluorinated β-amino acids is of particular interest in synthetic organic fluorine chemistry. The present protocol is difficult to be performed in a highly catalytic enantioselective manner due to the fast background reaction mentioned above. The issue of stereo-outcome of this aza-Michael addition could be effectively addressed by the use of a chiral oxazolidinone auxiliary. In a scale-up reaction between the chiral acrylate **4** (4 mmol) and amine **2k** (Scheme 2), the major diastereomer (*S*,*R*)-**5** was obtained pure in a 68% yield, based on the recovered starting material (brsm), after chromatographic separation of the diastereomeric mixture (dr = 2.8). An important advantage of the present chemistry is that the aza-Michael adduct **5** could be easily hydrolyzed into enantioenriched TFAA **6** with LiOH-H_2O_2. With **6** in hand, the access to two enantiomerically pure heterocycles with a CF_3 group at the chiral tertiary carbon center was elaborated. Chiral 2-CF_3-2,3-dihydro-1*H*-quinolin-4-one **7**, serving as a building block for creating trifluoromethlyated analogues of dihydroquinolinone



Scheme 2 Synthetic utility of chiral β-CF_3 β-amino acid **6**.

or tetrahydroquinoline type drugs,[15] was successfully installed *via* a polyphosphoric acid (PPA)-promoted intramolecular Friedel–Crafts reaction.[16] Furthermore, the β-CF_3 β-amino ester **8** derived from **6** was cyclized in the presence of CH_3MgBr to construct enantioenriched trifluoromethylated β-lactam **9** in 69% yield, which represents the key part of an ezetimibe analogue as a potent inhibitor of cholesterol absorption. The absolute stereochemistry of **9** was determined as *S* by comparison of the optical rotation with that found in the literature,[4b] so the configurations of compounds **6** and **7** were both assigned as *S*.

The features of the present aza-Michael addition are summarized as follows: (1) this study represents the first example of building TFAA derivatives *via* aza-Michael addition in a highly environmentally benign and atom-economic fashion; (2) fluorinated groups at the β-position of electrophiles are critical for the efficient transformation; (3) benzylhydrazine as a bis-nucleophile generated a trifluoromethylated pyrazolidinone (5-membered ring) *via* a novel cascade aza-Michael/amidolysis cyclization reaction; (4) the reported green process is a potentially practical and generalized approach. It has been easily and successfully scaled-up to synthesize enantioenriched TFAAs, thereby, giving a rapid access to two structurally diverse chiral trifluoromethylated N-heterocycles (4- and 6-membered ring) in good yields. We will extend this green strategy to other research involving the expeditious construction of enantiomerically pure trifluoromethylated heterocycles. This investigation is underway in our laboratory.

Acknowledgements

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