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Enantioselective catalytic synthesis of α-aryl-α-SCF_3-$\beta^{2,2}$-amino acids†

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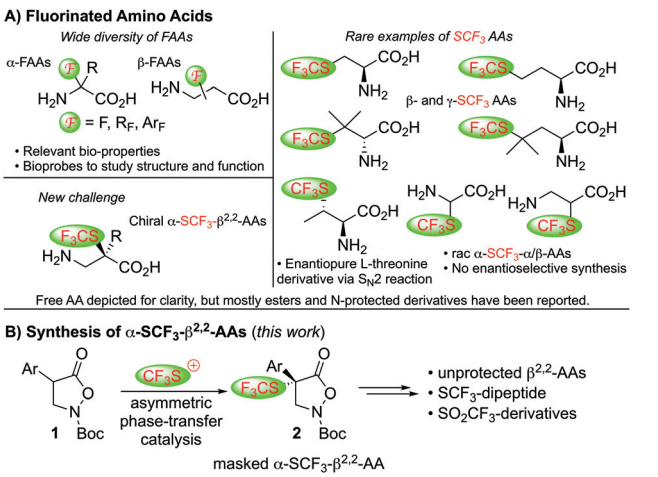
We herein report a novel entry towards chiral α-SCF_3-$\beta^{2,2}$-amino acids by carrying out the ammonium salt-catalyzed α-trifluoromethylthiolation of isoxazolidin-5-ones. This approach allowed for high enantioselectivities and high yields and the obtained heterocycles proved to be versatile platforms to access other targets of potential interest.

While nature employs only twenty-two genetically encoded proteinogenic amino acids (AAs) as vital building blocks for life, a plethora of chemically synthesized unnatural AAs exists. In principle, the later offer infinite tools to expand the genetic code and to investigate protein's structure and function. Of particular importance, fluorinated amino acids (FAAs) fall within the realm of specific investigations related to structural and functional learning of peptidic compounds.[1] The introduction of a single fluorine atom or a CF_3 motif are common approaches to obtain FAAs,[2] whereas the supply of alternative F-containing motifs remains much less-explored (Scheme 1A). The incorporation of the highly lipophilic trifluoromethylthio group CF_3S into amino acids (and subsequent peptides) should be beneficial for the elucidation of structure and function, as well as for pharmaceutical developments. Indeed, as analogues of the sulfur-containing methionine and cysteine, SCF_3-derivatives should help to escape the hydrophobic core where thiol residues are usually buried while ensuring protection against oxidation. Furthermore, thanks to the power of ^{19}F NMR techniques and some recently developed ^{18}F-radiolabeling strategies of the CF_3S group, the site-specific installation of trifluoromethylthio amino acids (SCF_3-AAs) to probe local events in peptides is a powerful tool to investigate structure and function in a complementary fashion.[3]

The common strategy to access SCF_3-AAs, relies on the trifluoromethylation of thiols[4] or disulfides.[5] As for the direct introduction of the whole CF_3S motif in AAs, rare examples include regioselective trifluoromethylthiolation of unactivated C–H bonds of amino esters,[6] electrophilic α-trifluoromethylthiolation of glycine Schiff bases,[7a] aminotrifluoromethylthiolation of α,β-unsaturated carbonyl compounds[7b] and nucleophilic trifluoromethylthiolation of a variety of cyclic sulfamidates based on a stereospecific S_N2-type process (*i.e.* this strategy developed by one of us gives access to an enantiopure L-threonine derivative where the OH-group is replaced for a CF_3S-group).[8] However, to the best of our knowledge, no enantioselective approach for the synthesis of chiral SCF_3-AAs was reported until now.[9]

The lack of enantioselective catalytic procedures to access novel SCF_3-AAs led us to study the construction of $\beta^{2,2}$-AAs featuring the CF_3S motif at the tetrasubstituted non-racemizable stereocenter.[10] β-AA have attracted considerable attention over the last years,[11] and more recently the easily accessible



Scheme 1 (A) Overview of FAAs and SCF_3-AAs; (B) targeted asymmetric α-SCF_3-$\beta^{2,2}$-AA syntheses starting from α-aryl-isoxazolidin-5-ones **1**.

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α-substituted isoxazolidin-5-ones **1** [12] (as masked β^2-AAs) have gained significant interest as precursors for $\beta^{2,2}$-AA derivatives.[9,13–15] Especially, the use of asymmetric phase-transfer catalysis (PTC), by means of chiral quaternary ammonium salt ion pairing catalysts,[16] allowed highly enantioselective α-functionalization reactions of **1** towards α,α-disubstituted isoxazolidin-5-ones **2**, albeit with a limited number of electrophiles so far (compounds **1** and **2** in Scheme 1B show the specific substitution patterns we wish to investigate herein but several other derivatives have been reported recently). Importantly, this masked $\beta^{2,2}$-AA derivatives can then undergo facile reductive ring-opening reactions to give $\beta^{2,2}$-AA derivatives[14,15] or may be directly incorporated into peptides by means of the so-called KAHA ligation technique.[14d,15a,17]

Based on our recent progress in the utilization of compounds **1** to access masked chiral $\beta^{2,2}$-AAs **2** under chiral phase-transfer catalysis,[14] we now became interested in introducing an asymmetric protocol to access novel α-SCF_3-α-aryl-substituted targets **2** by carrying out the electrophilic trifluoromethylthiolation of α-aryl-**1** under chiral ammonium salt catalysis (Scheme 1B). The hereby obtained masked SCF_3-$\beta^{2,2}$-AAs **2** represent a unique entry to SCF_3-$\beta^{2,2}$-AAs, dipeptides or the corresponding SO_2CF_3-analogs.

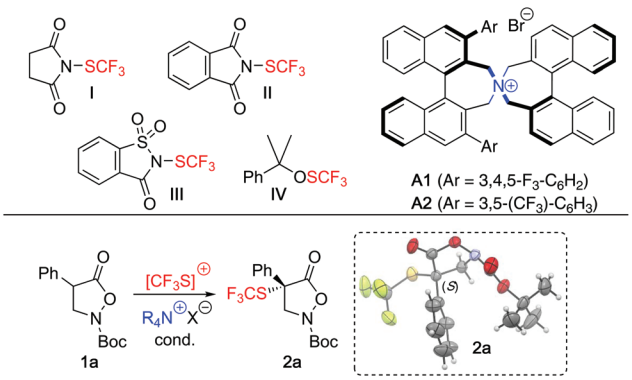
We started our investigations by carrying out the α-trifluoromethylthiolation of the phenyl-substituted **1a** with the established electrophilic CF_3S-transfer reagents **I–IV** [18] using Maruoka's catalysts **A** [19] (Table 1 gives an overview of the most significant results of a broad and systematic screening). It should be noted that other chiral ammonium salt catalysts were tried as well, but in analogy to our recent observations,[14] none of these quaternary ammonium salts led to useful enantioselectivities.[20]

First experiments with catalyst **A2** and the succinimide-based reagent **I** allowed for a promising initial enantiomeric ratio of 82 : 18 already (entry 1). In addition, reagent **I** performs slightly better than the phthalimide-based **II**, while neither the saccharin-derived **III** nor the cumyl O-SCF_3 reagent **IV** did allow for any product formation at all (entries 1–4). Using the catalyst **A1**, substituted by the 3,4,5-trifluorophenyl pendant at 3,3′-positions, a slight increase in enantioselectivity could be achieved, combined with lowering the excess of reagent **I** (entry 5). Even more interestingly, the reaction allowed the use of catalytic amounts of base, without affecting the enantioselectivity (entry 6). The evaluation of different solvents showed that ethers in general furnished higher selectivities than aromatic or chlorinated solvents (entries 6–10). As Et_2O performed slightly better than other ethers, the base-optimization was performed in Et_2O subsequently (entries 11–13). Noteworthy, the nature of the base did not affect the enantioselectivity significantly, contrary to the yield.

As the base can be used catalytically in these reactions, which is rather similar to our recent observations for asymmetric α-sulfanylation reactions of compounds **1**,[14a] it can be rationalized that the *in situ* formed K-succinimide may also serve as a base during these reactions (thus rationalizing why different bases resulted in more or less the same enantioselectivities). Then, we carried out one reaction using a catalytic amount of K-phthalimide under the final optimized conditions (*vide infra*) and the observed selectivity and yield were exactly the same, thus substantiating this mechanistic proposal.

As K_2HPO_4 gave somewhat higher yields than the other bases (entry 13), we carried out the final optimization with this base in Et_2O. It turned out that lowering the reaction temperature to −20 °C, with a slightly higher dilution and slow addition of **I** provided enantioselectivities up to 95 : 5 (entries 15 and 16). To our delight, product **2a** can be further enantioenriched by recrystallization and can also easily be accessed on 1 mmol scale with 3 mol% of catalyst **A1** in high yield and enantioselectivity (entry 17) (lower catalyst loadings then lead to significantly reduced conversions). The absolute configuration of product **2a** was unambiguously assigned by single

Table 1 Identification of the best-suited SCF_3-transfer reagent, catalyst and conditions for the synthesis of **2a**[a]



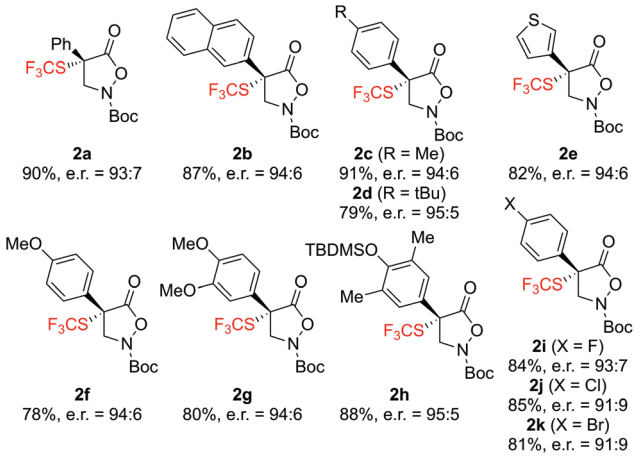
Entry	Cat. (mol%)	$[CF_3S]^+$ (eq.)	Solv.	Base (eq.)	Yield[b] [%]	e.r.[c] (*S* : *R*)[d]
1	**A2** (5)	**I** (3)	Et_2O	Cs_2CO_3 (2)	80	82 : 18
2	**A2** (5)	**II** (3)	Et_2O	Cs_2CO_3 (1.1)	70	75 : 25
3	**A2** (5)	**III** (3)	Et_2O	Cs_2CO_3 (1.1)	0	—
4	**A2** (5)	**IV** (3)	Et_2O	Cs_2CO_3 (1.1)	0	—
5	**A1** (5)	**I** (1.5)	Et_2O	Cs_2CO_3 (1.1)	77	90 : 10
6	**A1** (5)	**I** (1.2)	Et_2O	K_2CO_3 (0.2)	89	89 : 11
7	**A1** (5)	**I** (1.2)	iPr_2O	K_2CO_3 (0.2)	85	87 : 13
8	**A1** (5)	**I** (1.2)	THF	K_2CO_3 (0.2)	66	76 : 24
9	**A1** (5)	**I** (1.2)	CH_2Cl_2	K_2CO_3 (0.2)	53	75 : 25
10	**A1** (5)	**I** (1.2)	$PhCH_3$	K_2CO_3 (0.2)	56	84 : 16
11	**A1** (5)	**I** (1.2)	Et_2O	KOAc (0.2)	25	90 : 10
12	**A1** (5)	**I** (1.2)	Et_2O	NaOPh (0.2)	71	89 : 11
13	**A1** (5)	**I** (1.2)	Et_2O	K_2HPO_4 (0.2)	88	90 : 10
14	**A1** (5)	**I** (1.05)	Et_2O[e]	K_2HPO_4 (0.2)	82	91 : 9
15[f]	**A1** (5)	**I** (1.05)	Et_2O[e]	K_2HPO_4 (0.2)	90	93 : 7 (98 : 2)[g]
16[f]	**A1** (5)	**I** (1.05)[h]	Et_2O[e]	K_2HPO_4 (0.2)	90	95 : 5
17[f,i]	**A1** (3)	**I** (1.05)	Et_2O[e]	K_2HPO_4 (0.2)	90	93 : 7

[a] All reactions were run for 20 h at room temperature using 0.1 mmol **1a** in the indicated solvent (0.1 M with respect to **1a**) with the given reagents and catalysts unless otherwise stated. [b] Isolated yields. [c] Determined by HPLC using a chiral stationary phase. [d] Absolute configuration was determined by X-ray diffraction analysis of single crystals of enantioenriched (*S*)-**2a**.[21] [e] 0.05 M with respect to **1a**. [f] Run at −20 °C. [g] After recrystallization. [h] Added with a syringe pump over 5 h. [i] 1 mmol scale.

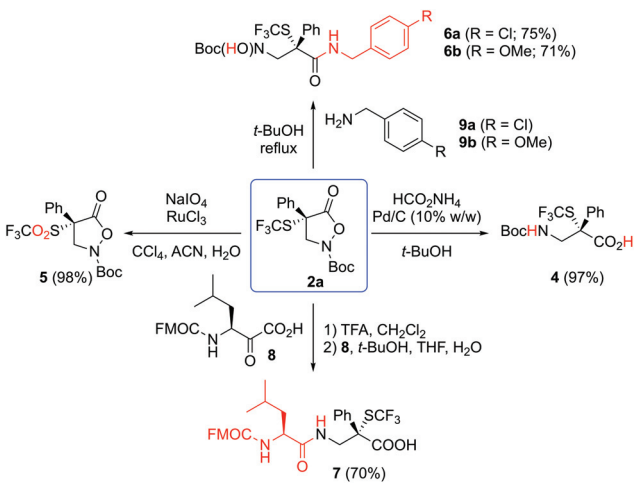
crystal X-ray analysis[21] and the sense of enantioinduction is in line with our previous observations using Maruoka catalysts **A** with pronucleophiles **1**.[14]

With high yielding and highly enantioselective catalytic conditions at hand, we next investigated the application scope of this approach for a variety of variously substituted α-aryl-derivatives **1** (Scheme 2). For ease of experimental operation, we carried out the trifluoromethylthiolation reactions under the conditions given in entry 15 (Table 1) avoiding the electrophile addition *via* syringe pump. As outlined in Scheme 2, a variety of novel masked α-SCF_3-α-aryl-$\beta^{2,2}$-AAs **2a–2k** were readily obtained in high yields and with satisfying enantiomeric ratios, ranging from 91 : 9 to 95 : 5 e.r., regardless of the nature of the aryl moiety.

To demonstrate the versatility of the herein accessed heterocyclic platform **2**, we also carried out the transformations of compound **2a** as depicted in Scheme 3. The N–O-bond could be easily cleaved under Pd-catalyzed hydrogenation conditions to afford the free carboxylic acid **4** in literally quantitative yield.[12,14] In addition, the CF_3S-group could be oxidized to the corresponding sulfone (giving product **5**) straightforwardly with $NaIO_4$ under $RuCl_3$-catalysis.[22] Furthermore, compound **2a** can directly be engaged into amide bond forming reactions by carrying out a nucleophilic ring opening reaction with benzylic amines to give compounds **6**. On the other hand, after a facile *N*-Boc deprotection of **2a**, the KAHA ligation[17] with reagent **8** occurred to give access to the corresponding dipeptide **7** under previously described aqueous-conditions.[14d,15a] All these performed transformations furnished high yields under robust reaction conditions, thus substantiating the synthetic versatility of our SCF_3-containing heterocyclic platform **2**.



Scheme 2 Application scope (all reactions were carried out on 0.1 mmol scale under the conditions given in Table 1, entry 15).



Scheme 3 Further transformations of compound **2a**.

Conclusions

We have shown that α-aryl-isoxazolidin-5-ones **1** can undergo α-trifluoromethylthiolation reactions with high enantiomeric excesses and excellent yields under asymmetric phase-transfer catalysis conditions by using the commercially available Maruoka catalyst **A1**.[9] These α-heterofunctionalization reactions perform under operationally simple conditions and could easily be carried out on 1 mmol scale as well. In addition, the hereby accessed masked α-SCF_3-$\beta^{2,2}$-AAs **2** can be utilized to obtain unprotected α-SCF_3-$\beta^{2,2}$-AAs, amides, dipeptides and the corresponding SO_2CF_3-analogs either.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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9 During the submission of this article Della Sala, Aleman and co-workers independently reported the chiral ammonium salt-catalyzed α-trifluoromethylthiolation of isoxazolidin-5-ones **1** essentially with α-benzyl pendants in good to moderate yields and with high enantioselectivities. They also reported two α-aryl derivatives, which however performed less selectively. Under our conditions α-benzyl-derivatives **1** did not react, but, as a complementary approach, we succeeded in the elaboration of α-aryl-containing **1** with high yields and enantiomeric ratios: V. Capaccio, M. Sicignano, R. I. Rodriguez, G. Della Sala and J. Aleman, *Org. Lett.*, 2020, **22**(1), 219–223.

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20 Further details can be found in the ESI.†

21 CCDC 1914375 contains the supplementary crystallographic data for **2a**.†

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