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Organocatalytic Asymmetric Addition of Thiols to Trifluoromethylaldimine: An Efficient Approach to Chiral Trifluoromethylated *N*,*S*-Acetals

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Abstract: The first organocatalytic asymmetric addition of thiols to trifluoromethylaldimine for the construction of chiral trifluoromethylated *N*,*S*-acetals has been achieved in high yields (up to 99%) and excellent enantioselectivities (up to 95% *ee*) with 1 mol% of a bifunctional organocatalyst.

Keywords: asymmetric catalysis; bifunctional organocatalysts; enantioselectivity; *N*,*S*-acetals; trifluoromethyl group

Organofluorine compounds have attracted considerable attention in pharmaceutical, agrochemical and material research as a result of the beneficial properties brought by the fluorine atom.[1] Trifluoromethyl-containing compounds are of great interest in various fields because of the high electronegativity and specific properties. On the other hand, the introduction of a trifluoromethyl group in biologically active molecules has become an important strategy for increasing the biological activity of a molecule, since the presence of the trifluoromethyl moiety may assist drug absorption, modify its tissue distribution, and significantly change preferred molecular conformations.[2] Among various trifluoromethyl-containing compounds, trifluoromethylated amines are of primary significance since these privileged chiral synthons have high potential as core elements for the development of related compounds leading to medicinal agents[3] and exhibit interesting biological activity as exemplified by compounds **1**–**3**[4] shown in Figure 1. Enantiomerically enriched sulfur-containing compounds also exhibit important applications in many areas of chemistry and biology.[5] Chiral *N*,*S*-acetals are common structural motifs present in numerous biologically important natural products,[6] such as the fusaperazine A (**4**) and (+)-11,11′-dideoxyverticillin A (**5**) (Figure 1).[7] In sharp contrast to the well-documented approaches to access either trifluoromethylated compounds[1–3] or sulfur-containing compounds,[5,6] the development of effective method for the catalytic asymmetric construction of the trifluoromethylated *N*,*S*-acetal motif still remains elusive.

Recently, Antilla and co-workers developed an elegant organocatalyzed addition reaction of thiols to highly active *N*-acylimines leading to the asymmetric synthesis of chiral *N*,*S*-acetals in excellent yields and enantioselectivities.[8] Most recently, we reported the first asymmetric sulfa-Michael addition of thiols to trifluoromethylated electron-deficient alkenes catalyzed by a bifunctional amine-thiourea, which serves as a generally efficient protocol for the direct construction of chiral building blocks bearing a unique trifluoromethyl group and a sulfur atom at the stereogenic center.[9]

Encouraged by these achievements, we envisioned that an acid-base bifunctional organocatalyst[10] could efficiently enhance the nucleophilicity of the thiol and

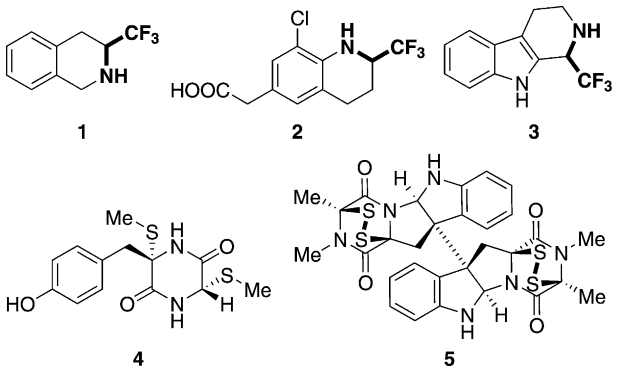
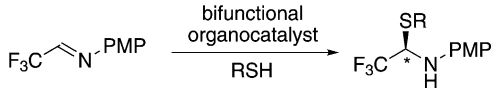


Figure 1. Examples of biologically important molecules containing privileged trifluoromethylamine and chiral *N*,*S*-acetal motifs.



Scheme 1. Asymmetric addition of thiols to trifluoromethylaldimines.

simultaneously activate the trifluoromethylated aldimine through hydrogen bonding interactions with the imino group, and thereby realize the challenging target of trifluoromethylated *N,S*-acetals with high enantioselectivity (Scheme 1). Herein, we would like to document a highly enantioselective addition of thiols to trifluoromethyl aldimine catalyzed by a bifunctional squaramide-based organocatalyst with as low as to 1 mol% catalyst loading, providing trifluoromethylated *N,S*-acetals in high yields and excellent enantioselectivities.

We began our investigation by examining the catalytic asymmetric addition of benzyl mercaptan **2a** to trifluoromethylated aldimine **1a** in dichloromethane at room temperature with bifunctional organocatalysts derived from 1,2-diaminocyclohexane or *Cinchona* alkaloids (Figure 2).[11] To our delight, this addition reaction proceed efficiently in less than 30 min with the commonly used bifunctional amine-thioureas affording the expected adducts in high yields albeit with moderate enantioselectivities (50–77% *ee*) (Table 1, entries 1–5). To further improve the enantioselectivity,

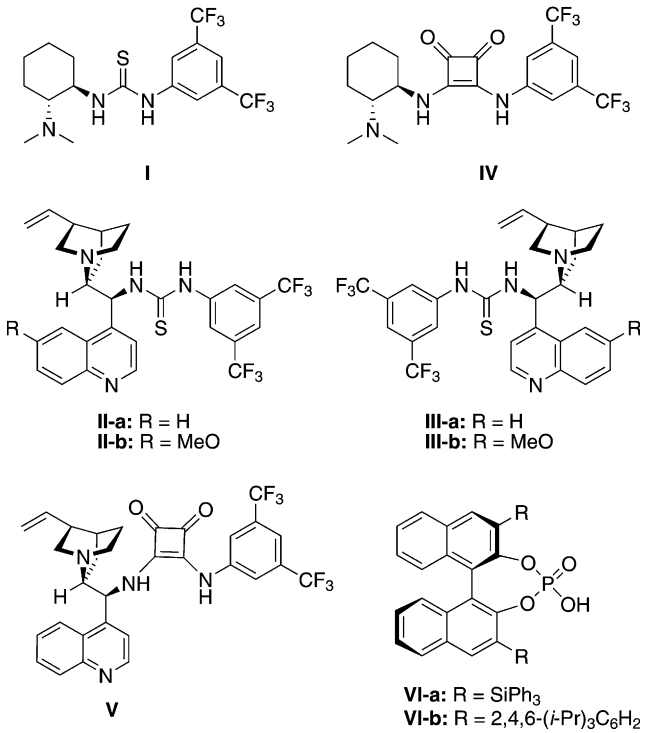
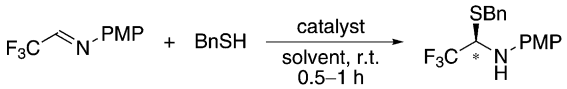


Figure 2. Structures of the screened bifunctional organocatalysts.

Table 1. Screening of reaction conditions for the addition of benzyl mercaptan **2a** to trifluoromethylated aldimine **1a** catalyzed by bifunctional organocatalysts.[a]



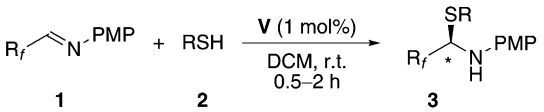
1a **2a** **3a**

Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	**I** (10 mol%)	DCM	96	77
2	**II-a** (10 mol%)	DCM	97	75
3	**II-b** (10 mol%)	DCM	94	75
4	**III-a** (10 mol%)	DCM	92	50
5	**III-b** (10 mol%)	DCM	93	58
6	**IV** (10 mol%)	DCM	94	74
7	**V** (10 mol%)	DCM	98	93
8[d]	**VI-a** (10 mol%)	DCM	96	6
9[d]	**VI-b** (10 mol%)	DCM	94	65
10	**V** (10 mol%)	ether	90	85
11	**V** (10 mol%)	PhMe	95	92
12	**V** (10 mol%)	MeCN	94	78
13	**V** (10 mol%)	MeOH	92	2
14[e]	**V** (10 mol%)	DCM	95	88
15	**V** (5 mol%)	DCM	96	93
16	**V** (1 mol%)	DCM	98	94

[a] All reactions were carried out with 0.20 mmol of **1a**, 0.24 mmol of **2a** in 0.5 mL of solvent. PMP = *p*-methoxyphenyl.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Carried out in PhMe within 20 h.
[e] Carried out at 0 °C.

we turned our attention toward the use of chiral 1,2-diaminocyclohexane and *Cinchona* alkaloids-derived squaramides as the H-bonding motif[12] since they had been demonstrated to be efficient for a variety of asymmetric transformations.[13] Gratifyingly, a significant increase of enantioselectivity was achieved when cinchonidine-derived squaramide catalyst **V** was employed as the bifunctional catalyst (entry 7). Chiral BINOL-derived phosphoric acids **VI-a** and **VI-b**, which exhibited excellent results in the addition reaction of thiols to highly active *N*-acylimines,[8] were also tested in this transformation. However, a much lower catalytic activity was observed together with a relatively poor enantiomeric excess (entries 8 and 9). Subsequent screening of solvents showed that the reaction media had a significant effect on the enantioselectivity. Less polar solvents such as DCM, toluene, and ether were superior to polar and protic solvents (entries 7 and 10–13), and DCM gave the best results in terms of the yield and the enantioselectivity. Reducing the reaction temperature to 0 °C has no effect on the yield, but a slightly decrease on the enantioselectivity (entry 14). Remarkably, high yield and enantioselectivity and fast reaction rate were maintained

Table 2. Asymmetric addition of various thiols **2** to fluorinated aldimines **1** with organocatalyst **V**.[a]



1 2 3

Entry	R_f	R	Product	Yield [%][b]	*ee* [%][c]
1	CF_3 (**1a**)	Bn (**2a**)	**3a**	98	94
2	CF_3 (**1a**)	4-Cl-Bn (**2b**)	**3b**	95	93
3	CF_3 (**1a**)	4-MeO-Bn (**2c**)	**3c**	96	91
4	CF_3 (**1a**)	Et (**2d**)	**3d**	98	94
5	CF_3 (**1a**)	*n*-Pr (**2e**)	**3e**	99	93
6	CF_3 (**1a**)	*i*-Pr (**2f**)	**3f**	97	95
7	CF_3 (**1a**)	*i*-Bu (**2g**)	**3g**	93	92
8[d]	CF_3 (**1a**)	*t*-Bu (**2h**)	**3h**	90	94
9	CF_3 (**1a**)	*i*-amyl (**2i**)	**3i**	94	91
10	CF_3 (**1a**)	dodecyl (**2j**)	**3j**	92	90
11	CF_3 (**1a**)	cyclopentyl (**2k**)	**3k**	95	95
12	CF_3 (**1a**)	cyclohexyl (**2l**)	**3l**	93	94
13	CF_3 (**1a**)	allyl (**2m**)	**3m**	94	90
14	CF_3 (**1a**)	2-phenylethyl (**2n**)	**3n**	92	90
15	CF_3 (**1a**)	furfuryl (**2o**)	**3o**	95	90
16	$CClF_2$ (**1b**)	Bn (**2a**)	**3p**	93	85
17	$CBrF_2$ (**1c**)	Bn (**2a**)	**3q**	92	86
18[e]	CF_3 (**1a**)	Ph (**2p**)	**3r**	96	70

[a] All reactions were carried out with 0.20 mmol of **1**, 0.24 mmol of **2** in 0.5 mL of DCM.
[b] Yield of the isolated products **3** after chromatographic purification.
[c] Determined by HPLC analysis.
[d] Reaction time: 48 h.
[e] Reaction time: 10 min.

even when the reaction was performed with as low as 1 mol% of catalyst loading (entry 16).

With the optimal reaction conditions in hand, an array of thiols was tested to investigate the generality of this reaction, and the results are summarized in Table 2. Substituted benzyl thiols bearing electron-rich, electron-neutral, or electron-deficient groups on the aromatic ring reacted smoothly with trifluoromethylated aldimine **1a** to afford the expected adducts (**3a–3c**) with high yields and excellent enantioselectivities (91–94%) (Table 2, entries 1–3). Heteroaromatic furfuryl mercaptan **2o** also work well in this transformation leading to the corresponding adduct in 90% *ee* (entry 15). To further probe the steric effects of substituent on this catalytic system, various alkyl thiols with branched and sterically bulky substituents were employed. Primary alkyl thiols with *n*-alkyl substituents such as ethyl, *n*-propyl, and 2-phenylethyl group all have afforded high yields and excellent enantioselectivities (entries 4, 5 and 14). Allyl thiol **2m** was also a viable nucleophile as were the branched isobutyl thiol **2g** and isoamyl thiol **2i** (entries 7, 9 and 13). Noticeably, for alkyl thiol **2j** with the longer carbon chain *n*-$C_{12}H_{25}$, high reactivity and enantioselectivity were still maintained at the similar level (entry 10). Secondary thiols either with an acyclic isopropyl group or with cyclic groups such as cyclohexyl and cyclopentyl were also tested, and excellent enantioselectivity and reaction rate were observed for each case (entries 6, 11 and 12). The consistently excellent enantioselectivity obtained with the tertiary *tert*-butyl thiol **2h** is noteworthy (entry 8), as such a sterically hindered tertiary thiol was shown to be a relatively challenging nucleophile in previous studies,[13h] although a longer reaction time was need to maintain the high yield. Chlorodifluoromethylated aldimine **1b** and bromodifluoromethylated aldimine **1c** also worked well affording the expected adducts in high yields with good enantioselectivities (entries 16 and 17). Aromatic thiol **2p** also exhibited high reactivity in this reaction affording a good yield albeit with a moderate enantioselectivity[14] (entry 18).

The absolute configuration of the trifluoromethylated *N*,*S*-acetal **3c** was determined unambiguously to be *R* by a single X-ray crystallographic analysis (Figure 3).[15] Those of other adducts were tentatively proposed on the basis of these results.

To examine the mechanism for this addition reaction, we carried out NMR studies of the substrate–catalyst combination. Mixing an equal amount of **1a** with catalyst **V** in $CDCl_3$ resulted in no significant change of the resonances (^{1}H NMR and ^{19}F NMR analysis), which indicates that the non-covalent interactions of them are probably very weak.[16] A similar phenomenon has been noticed by Jacobsen for the Strecker reaction.[17] Nearly racemic adduct **3a** was obtained when methanol was employed as reaction solvent, since solvation of methanol to the imino group of **1a** might disturb the hydrogen bonding interaction between **V** and **1a**. The same experiment was also studied for a mixture of thiol **2a** and **V**, and the ^{1}H NMR spectrum revealed that **2a** is deprotonated by the tertiary amine of the catalyst.[16] Based on the above experimental results and the absolute configu-

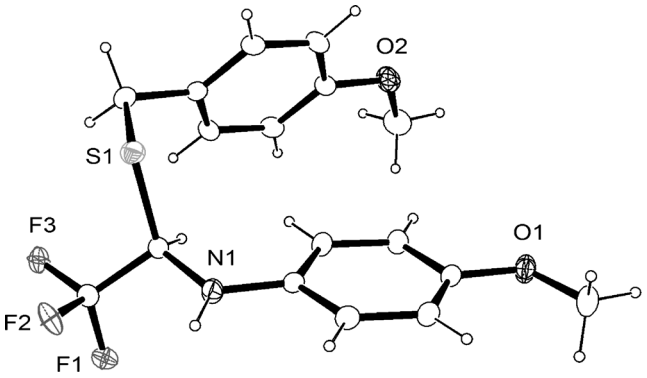


Figure 3. X-ray crystallographic structure of (*R*)-**3c**.

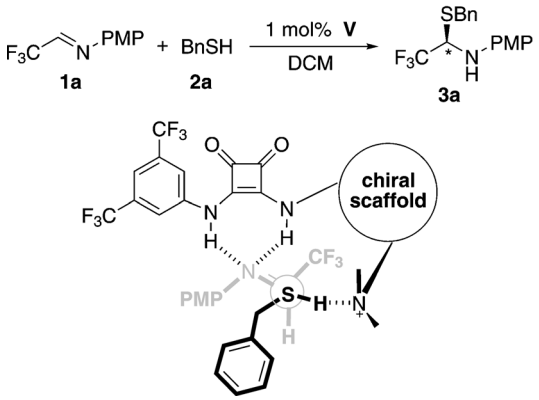


Figure 4. Proposed transition state model leading to the (*R*)-adduct.

ration of (*R*)-**3c**, a plausible dual activation model accounting for the observed stereoselectivity of the addition of thiols to trifluoromethylated aldimine is shown in Figure 4, in which the squaramide moiety interacts through hydrogen bonding with trifluoromethylated aldimine and enhances the reactivity toward nucleophilic attack while the neighbouring tertiary amine serves as a general base to enhance the nucleophilicity of the thiol simultaneously. The attack of the thiol to the *Re*-face of trifluoromethylated aldimine affords the corresponding (*R*)-adduct, which is compatible with the experimental results.

In conclusion, we have developed the first highly efficient asymmetric addition of thiols to fluorinated aldimines catalyzed by a chiral squaramide-based organocatalyst. This present method serves as a powerful approach to a new family of biologically important trifluoromethylated *N*,*S*-acetals in high yields and excellent enantioselectivities. Further investigations on the scope and synthetic application of this methodology are ongoing.

Experimental Section

General Procedure for Catalytic Asymmetric Addition of Thiols to Fluorinated Aldimines

To a vial containing fluorinated aldimine **1** (0.20 mmol) and catalyst **V** (1.2 mg, 0.002 mmol) in DCM (0.5 mL) was added thiol **2** (0.24 mmol) at room temperature. The resulting reaction mixture was kept under vigorous stirring until consumption of **1** (as monitored by TLC analysis). The reaction solution was then concentrated under vacuum and the residue was purified by flash chromatography on silica gel to afford the corresponding product **3**, which was then directly analyzed by HPLC analysis to determine the enantiomeric excess.

Acknowledgements

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[14] Trials to remove the PMP group in the trifluoromethylated *N*,*S*-acetals **3** failed probably due to the unstability of the corresponding unprotected *N*,*S*-acetals.

[15] Crystal data for (*R*)-**3c**: $C_{17}H_{18}F_3NO_2S$, $M_r = 357.38$, $T = 293$ K, monoclinic, space group $P2(1)$, $a = 7.9306(14)$, $b = 5.5541(10)$, $c = 19.245(3)$ Å, $V = 847.2(3)$ Å^3, $Z = 2$, 3340 unique reflections, final $R_1 = 0.0309$ and $wR_2 = 0.0729$ for 3038 observed [$I > 2\sigma(I)$] reflections, Flack $\chi = -0.02(7)$. CCDC 884508 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)-1223-336-033; or deposit@ccdc.cam.ac.uk].

[16] See the Supporting Information for more details.

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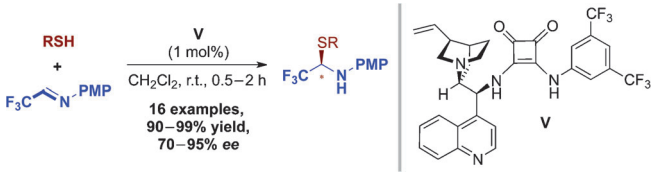

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