Tetrahedron Letters 54 (2013) 4509–4511

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Organocatalytic asymmetric sulfa-Michael addition of thiols to *trans*-3,3,3-trifluoropropenyl phenyl sulfone

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ARTICLE INFO

Article history:
Received 22 April 2013
Revised 28 May 2013
Accepted 13 June 2013
Available online 20 June 2013

Keywords:
Amine–thiourea catalyst
Asymmetric catalysis
Sulfa-Michael addition
trans-3,3,3-Trifluoropropenyl phenyl sulfone
Trifluoromethyl group

ABSTRACT

The first asymmetric sulfa-Michael addition of thiols to *trans*-3,3,3-trifluoropropenyl phenyl sulfone for the construction of a unique stereogenic center bearing a trifluoromethyl group and a sulfur atom has been achieved in high yields and moderate to good enantioselectivities with 1 mol % bifunctional amine–thiourea catalyst.

Incorporation of fluorine atoms into a stereogenic carbon center has attracted considerable attention mainly owing to the outstanding applications of chiral fluorinated organic compounds in various fields, including pharmaceuticals, agrochemicals, and materials.[1] Among organofluorine molecules, the trifluoromethyl group is frequently encountered in a lot of biologically active medicinal and agricultural compounds presumptively due to its intrinsic properties.[2] It always leads to tremendous changes in physical, chemical, and/or biological properties compared with non-fluorinated compounds, such as increasing lipophilicity, metabolic stability, and biological activity.[3] Sulfones are valuable intermediates in organic synthesis,[4] meanwhile, enantiomerically enriched sulfones bearing β-stereocenter are the key skeletons of complex natural or biologically important molecules.[5] Most recently, we have developed the first sulfa-Michael addition of thiols to *cis*-ethyl 4,4,4-trifluorocrotonate[6] and *trans*-4,4,4-trifluorocrotonoyl-pyrazole[7] catalyzed by a bifunctional amine–thiourea catalyst, which provided a straightforward and effective synthetic route to chiral building blocks bearing the trifluoromethyl group and sulfur atom at the stereogenic center. We envisioned that the sulfa-Michael addition of thiols to *trans*-3,3,3-trifluoropropenyl phenyl sulfone could provide a general method to afford chiral sulfones bearing a unique trifluoromethyl group. To the best of our knowledge, there was no example of the asymmetric sulfa-Michael addition of thiols to *trans*-3,3,3-trifluoropropenyl phenyl sulfone so far.[8] Herein, we reported the first catalytic asymmetric sulfa-Michael addition of thiols to *trans*-3,3,3-trifluoropropenyl phenyl sulfone catalyzed by a bifunctional amine–thiourea in high yields with moderate to good enantioselectivities (up to 84% ee).

Our initial investigation began with the sulfa-Michael addition of thiophenol **1a** to *trans*-3,3,3-trifluoropropenyl phenyl sulfone **2** in dichloromethane at room temperature in the presence of 10 mol % bifunctional amine–thiourea catalysts (Fig. 1), and the results are summarized in Table 1. In general, the reactions were efficiently completed in less than 10 min yielding the desired adduct **3a** in good to high yields. The fine-tunable amine–thiourea catalysts **I** and **II** bearing multiple hydrogen bonding donors developed in this lab[9] were screened in this reaction (Table 1, entries 1–8). To our delight, catalyst **II-c** exhibited the best results and the adduct **3a** was obtained in 90% yield and 50% ee (entry 7). Other commonly used chiral bifunctional amine–thiourea catalysts derived from 1,2-diaminocyclohexane[10] or cinchona alkaloids[11] were also tested in this transformation, producing the adduct with little lower enantioselectivities (entries 9–13).

The effects of solvent, reaction temperature, and catalyst loading were also investigated. The reaction displayed much lower enantiomeric excesses in polar solvents such as THF, MeCN, and MeOH (Table 2, entries 4, 7, and 8). On the contrary, the reaction was promoted efficiently in non-polar or less polar solvents, such as CH_2Cl_2, $CHCl_3$, Et_2O, and PhMe, delivering the Michael adduct with higher enantioselectivities (entries 1–3 and 6), and CH_2Cl_2 was the best solvent of choice. Reducing the reaction temperature

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http://dx.doi.org/10.1016/j.tetlet.2013.06.059

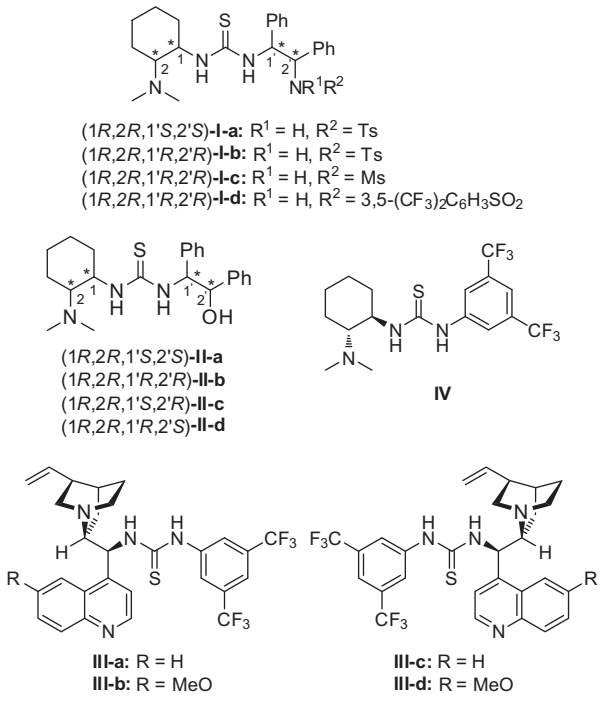
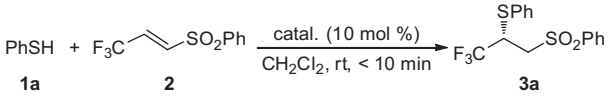


Figure 1. Screened bifunctional amine–thiourea organocatalysts (**I**–**IV**).

Table 1
Screening studies of sulfa-Michael addition of thiophenol **1a** to *trans*-3,3,3-trifluoropropenyl phenyl sulfone **2** catalyzed by bifunctional amine–thiourea catalysts[a]



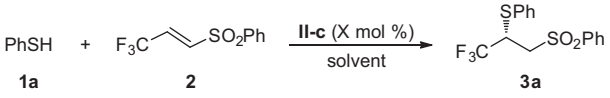
Entry	Catal.	Yield[b] (%)	ee[c] (%)
1	**I-a**	86	14
2	**I-b**	90	−22
3	**I-c**	86	−15
4	**I-d**	88	−25
5	**II-a**	86	11
6	**II-b**	83	1
7	**II-c**	90	50
8	**II-d**	79	−3
9	**III-a**	79	6
10	**III-b**	85	−10
11	**III-c**	82	−12
12	**III-d**	89	6
13	**IV**	96	26

[a] Unless otherwise noted, the reaction was carried out with 0.12 mmol of **1a** and 0.10 mmol of **2** in 0.5 mL of CH_2Cl_2.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

from room temperature to 0 °C and −20 °C improved the enantioselectivity to 56% and 64% ee, respectively (entries 9 and 10). Further reducing the reaction temperature could not lead to better enantioselectivity (entries 11 and 12). Decreasing the catalyst loading from 10 to 1 mol % did not result in the loss of either the yield or enantioselectivity (entries 13 and 14).

Encouraged by this result, we turned our attention to the scope and generality of this new asymmetric sulfa-Michael addition of thiols **1** to *trans*-3,3,3-trifluoropropenyl phenyl sulfone **2** under the optimized reaction conditions. As shown in Table 3, various electron-rich, electron-neutral, and electron-deficient aryl thiols

Table 2
Screening studies of sulfa-Michael addition of thiophenol **1a** to *trans*-3,3,3-trifluoropropenyl phenyl sulfone **2** catalyzed by catalyst **II-c** in various solvents[a]

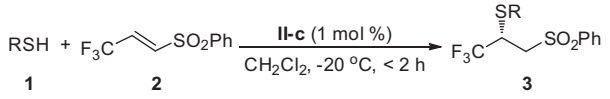


Entry	X mol %	*T* (°C)	Solvent	Time (min)	Yield[b] (%)	ee[c] (%)
1	10	rt	CH_2Cl_2	10	90	50
2	10	rt	$CHCl_3$	10	95	49
3	10	rt	Et_2O	10	84	32
4	10	rt	THF	10	66	12
5	10	rt	EtOAc	10	76	22
6	10	rt	PhMe	10	79	42
7	10	rt	MeCN	10	67	3
8	10	rt	MeOH	10	81	0
9	10	0	CH_2Cl_2	50	89	56
10	10	−20	CH_2Cl_2	100	95	64
11	10	−50	CH_2Cl_2	150	92	60
12	10	−78	CH_2Cl_2	300	90	58
13	5	−20	CH_2Cl_2	100	92	64
14[d]	1	−20	CH_2Cl_2	100	95	65

[a] Unless otherwise noted, the reaction was carried out with 0.12 mmol of **1a** and 0.10 mmol of **2** in 0.5 mL of solvent.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Carried out on a 0.25 mmol scale.

with different substitution patterns on the aromatic ring reacted smoothly with *trans*-3,3,3-trifluoropropenyl phenyl sulfone **2** to afford the adducts (**3a–3l**) in high yields (82–99%) with moderate to good enantioselectivities (44–84% ee) (Table 3, entries 1–12). Comparable results were still achieved for the sterically hindered *ortho*-methyl and *ortho*-fluoro substituted thiols **1b** and **1h** in terms of enantioselectivity and reactivity (entries 2 and 8). Among the tested nucleophiles, *ortho*-methoxy substituted thiol **1e** afforded the product with up to 84% ee (entry 5). Remarkably, the challenging and less reactive alkyl thiol **1m** also worked in this reaction and gave the desired adduct in good yield and morderate enantioselectivity (entry 13). The absolute configuration of the

Table 3
Asymmetric sulfa-Michael addition of thiols **1** to *trans*-3,3,3-trifluoropropenyl phenyl sulfone **2** with organocatalyst **II-c**[a]



Entry	R	**3**	Yield[b] (%)	ee[c] (%)
1	Ph (**1a**)	**3a**	95	65
2	*o*-Me–C_6H_4 (**1b**)	**3b**	87	64
3	*m*-Me–C_6H_4 (**1c**)	**3c**	82	57
4	*p*-Me–C_6H_4 (**1d**)	**3d**	93	48
5	*o*-MeO–C_6H_4 (**1e**)	**3e**	94	84
6	*m*-MeO–C_6H_4 (**1f**)	**3f**	99	49
7	*p*-MeO–C_6H_4 (**1g**)	**3g**	99	53
8	*o*-F–C_6H_4 (**1h**)	**3h**	83	64
9	*m*-F–C_6H_4 (**1i**)	**3i**	85	44
10	*p*-F–C_6H_4 (**1j**)	**3j**	89	47
11	2-Naphthyl (**1k**)	**3k**	83	49
12	4-^{t}Bu–C_6H_4 (**1l**)	**3l**	90	56
13	Bn (**1m**)	**3m**	82	36

[a] Unless otherwise noted, the reaction was carried out with 0.30 mmol of **1** and 0.25 mmol of **2** in 0.5 mL of CH_2Cl_2 at −20 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

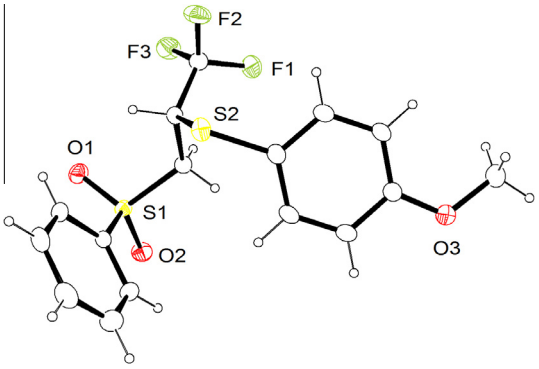


Figure 2. X-ray crystallographic structure of (*S*)-**3g**.

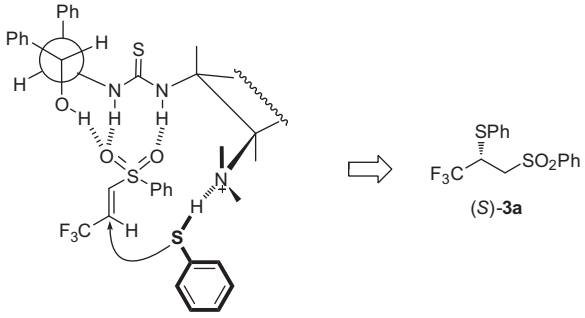


Figure 3. Proposed transition state model leading to (*S*)-adduct.

sulfa-Michael adduct **3g** was determined unambiguously to be *S* by single X-ray crystallographic analysis (Fig. 2).[12] Those of other adducts were tentatively proposed on the basis of these results.

Based on the absolute configuration of (*S*)-**3g**, a plausible dual activation model accounting for the observed stereoselectivity of the addition of thiols to *trans*-3,3,3-trifluoropropenyl phenyl sulfone is shown in Figure 3, in which the thiourea and hydroxy moieties interact through hydrogen bonding with *trans*-3,3,3-trifluoropropenyl phenyl sulfone and enhances their reactivity toward nucleophilic attack, while the neighboring tertiary amine serves as a general base to enhance the nucleophilicity of thiols simultaneously. The attack of the thiol to the *Si*-face of *trans*-3,3,3-trifluoropropenyl phenyl sulfone affords the corresponding (*S*)-adduct, which is compatible with the experimental results.

In conclusion, we have developed the first asymmetric sulfa-Michael addition of thiols to *trans*-3,3,3-trifluoropropenyl phenyl sulfone catalyzed by a bifunctional amine–thiourea catalyst bearing multiple hydrogen bonding donors. This catalytic system performed well over a broad scope of substrates and provided the desired sulfones bearing a unique trifluoromethyl group at the stereogenic center in high yields (82–99%) with moderate to good enantioselectivities (36–84% ee). Further investigations of the scope and synthetic applications of this methodology are ongoing, and the results will be reported in due course.

Acknowledgments

This work is supported by the NSFC (20972117), NCET-10-0649, IRT1030, and 973 Program (2011CB808600). We thank Professor Hua Li in Wuhan University for solving the crystal structure.

Supplementary data

Supplementary data (spectroscopic data of the compounds **3a**–**3m**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.059.

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12. CCDC 934845 (**3g**) contains the supplementary crystallographic data for this paper.