

Organocatalytic Asymmetric Sulfa-Michael Addition of Thiols to α,β -Unsaturated Hexafluoroisopropyl Esters: Expeditious Access to (*R*)-Thiazesim

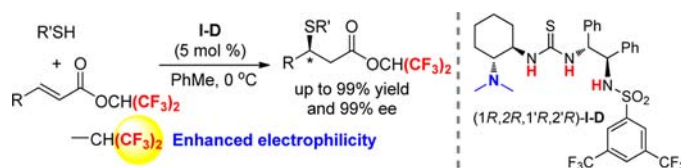
Xin Fang,[†] Jun Li,[†] and Chun-Jiang Wang^{*,†,‡}

College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, 430072, China, and State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin, 300071, China

cjwang@whu.edu.cn

Received May 30, 2013

ABSTRACT



A highly efficient organocatalytic asymmetric SMA reaction of hexafluoroisopropyl α,β -unsaturated esters has been developed. Introducing electron-withdrawing hexafluoroisopropyl ester is crucial to enhancing the electrophilicity of unsaturated esters as SMA acceptors. The catalytic system performs well over a broad scope of α,β -unsaturated esters and diversified thiols and provides facile access to (*R*)-thiazesim in a one-pot protocol.

Optically active chiral sulfur-containing compounds are the core structural elements prevalent in natural products¹ and also have broad applications in many research areas of biology and chemistry, for example, serving as antibiotics, chiral ligands or catalysts, and also chiral auxiliaries.² Among

existing methods, asymmetric sulfa-Michael addition (SMA) of thiol nucleophiles to electron-deficient alkenes is one of the most profound and reliable C–S bond-forming reactions in organic synthesis.³ Due to the simple manipulation and high atom economy, considerable attention has been paid to developing catalytic asymmetric protocols for SMA over the past several years.^{4,5} A variety of electron-deficient alkenes are now applicable as acceptors to both metal and organic catalyst-promoted conjugate additions, such as α,β -unsaturated imides,^{4a–f,5a–d} cyclic and acyclic enone,^{4g–j,5e–h} α,β -unsaturated aldehydes,⁵ⁱ and nitroolefins^{5j,k} (Scheme 1a).

[†] Wuhan University.

[‡] Nankai University.

(1) (a) Ondetti, M. A.; Rubin, B.; Cushman, D. W. *Science* **1977**, *196*, 441. (b) Kim, J.; Ashenurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238.

(2) (a) Nudelman, A. *The Chemistry of Optically Active Sulfur Compounds*; Gordon and Breach: New York, 1984. (b) Frausto da Silva, J. J. R.; Williams, R. J. P. *The Biological Chemistry of the Elements*; Oxford University Press: New York, 2001. (c) *Chiral Sulfur Ligands: Asymmetric Catalysis*; Pellissier, H., Ed.; Cambridge, U.K., 2009.

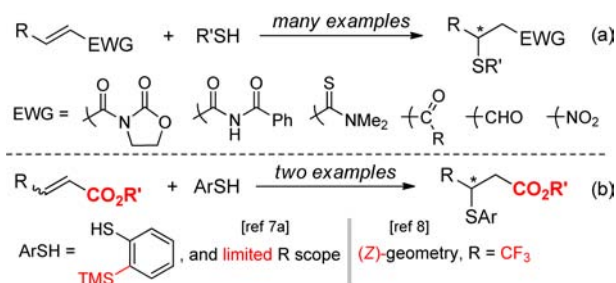
(3) For a review on asymmetric sulfa-Michael additions, see: Enders, D.; Lüttgen, K.; Narine, A. A. *Synthesis* **2007**, 959.

(4) For examples of organometallic-catalyzed asymmetric sulfa-Michael addition, see: (a) Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675. (b) Kobayashi, S.; Ogawa, C.; Kawamura, M.; Sugiura, M. *Synlett* **2001**, 983. (c) Matsumoto, K.; Watanabe, A.; Uchida, T.; Ogi, K.; Katsuki, T. *Tetrahedron Lett.* **2004**, *45*, 2385. (d) Abe, A. M. M.; Sauerland, S. J. K.; Koskinen, A. M. P. *J. Org. Chem.* **2007**, *72*, 5411. (e) Kawatsura, M.; Komatsu, Y.; Yamamoto, M.; Hayase, S.; Itoh, T. *Tetrahedron* **2008**, *64*, 3488. (f) Ogawa, T.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8551. (g) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043. (h) Emori, E.; Iida, T.; Shibasaki, M. *J. Org. Chem.* **1999**, *64*, 5318. (i) Badoiu, A.; Bernardinelli, G.; Besnard, C.; Kündig, E. P. *Org. Biomol. Chem.* **2010**, *8*, 193. (j) Hui, Y.-H.; Jiang, J.; Wang, W.-T.; Chen, W.-L.; Cai, Y.-F.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4290.

(5) For examples of organocatalyzed asymmetric sulfa-Michael addition, see: (a) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (b) Liu, Y.; Sun, B.-F.; Wang, B.-M.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 418. (c) Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem.* **2010**, *75*, 2089. (d) Rana, N. K.; Singh, V. K. *Org. Lett.* **2011**, *13*, 6520. (e) McDaid, P.; Chen, Y. G.; Deng, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 338. (f) Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth. Catal.* **2008**, *350*, 49. (g) Dai, L.; Wang, S.-X.; Chen, F.-E. *Adv. Synth. Catal.* **2010**, *352*, 2137. (h) Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 17934. (i) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (j) Li, H.; Wang, J.; Zu, L.-S.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 2585. (k) Kimmel, K.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754.

In light of the versatility of the reaction and biological activity of β -mercapto carboxylic acid derivatives,⁶ it is surprising that α,β -unsaturated esters, one of the cost-efficient Michael acceptors, have seldom been utilized in

Scheme 1. Reported Catalytic Asymmetric Sulfa-Michael Addition



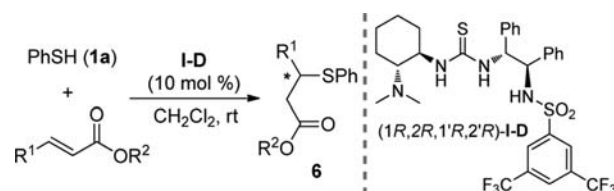
catalytic asymmetric SMA probably due to the relatively low electrophilicity. To our knowledge, there was only one example of α,β -unsaturated ester-involved asymmetric SMA catalyzed by a metal complex at low temperature;^{7a} however, the nucleophile was limited to *ortho*-substituted thiophenols and poor results were obtained for the electrophilic α,β -unsaturated esters with a branched chain or phenyl group at the β -position. Recently, an organocatalytic asymmetric SMA of thiols to *cis*-ethyl 4,4,4-trifluorocrotonate was reported by this laboratory; however, the σ -electron-withdrawing CF_3 group and synthetically difficult (*Z*)-geometry of the specific *cis*-4,4,4-trifluorocrotonate are the intrinsic limitations.⁸ Therefore, the development of a general synthetic protocol for the asymmetric SMA of thiols to easily available and diverse α,β -unsaturated esters is still a highly desirable and challenging goal in synthetic chemistry.

Considering the significant role the hexafluoroisopropyl ester moiety played in acrylate-involved asymmetric reactions⁹ and the role an acid–base bifunctional organocatalyst played in catalytic asymmetric synthesis,¹⁰ we envisaged that the electrophilicity of unsaturated esters could be enhanced by the electron-withdrawing hexafluoroisopropyl ester and

therefore improve its reactivity toward nucleophilic attack of thiols with good stereoselective control contributed by the H-bonding interactions between the substrates and catalyst and, hence, fulfill this important yet unsolved sulfa-Michael addition. Here, we describe a highly efficient organocatalyzed asymmetric sulfa-Michael addition of various thiols to a variety of α,β -unsaturated hexafluoroisopropyl esters. Furthermore, the current methodology was successfully applied to the concise synthesis of (*R*)-thiazesim.

In order to test our hypothesis, we first examined the reactivity of different α,β -unsaturated esters toward thiophenol (**1a**) attack to evaluate their electrophilicity in the presence of the amine-thiourea catalyst **I-D** developed in

Table 1. Ester Moiety Effect on Catalytic Asymmetric SMA of Thiophenol **1a** with Various α,β -Unsaturated Esters^a



entry	R ¹	R ²	time (h)	yield (%) ^b	ee (%) ^c
1	H	CH_2CH_3 (2)	0.2	95	-
2	Ph	CH_2CH_3 (3)	120	trace	-
3	Ph	CH_2CF_3 (4)	120	46	68
4	Ph	$\text{CH}(\text{CF}_3)_2$ (5a)	12	98	82

^a All reactions were carried out with 0.2 mmol of α,β -unsaturated ester and 0.24 mmol of thiophenol **1a** in 1 mL of CH_2Cl_2 . ^b Isolated yield. ^c Determined by HPLC analysis.

this laboratory recently,¹¹ and the results are shown in Table 1. Only a trace amount of adduct could be detected for ethyl cinnamate **3** even after 120 h, while less sterically hindered ethyl acrylate **2** exhibited high reactivity and the reaction finished quickly in < 10 min in high yield, which indicates that the β -substituent in unsaturated ester decreases its electrophilicity significantly due to unfavored steric hindrance (Table 1, entries 1 and 2). Replacing the ester functional group with the 2,2,2-trifluoroethyl group increases the electrophilicity of cinnamate, and the Michael adduct was separated in 46% yield with 68% ee although a long reaction time was still needed (entry 3), which preliminarily verifies our hypothesis on electrophilicity enhancement *via* introducing an electron-withdrawing ester moiety and enantioselective control *via* the synergistic H-bonding activation of both a Michael donor and acceptor. Subsequently, introducing a bulkier and more

(6) For applications of β -mercapto carboxylic acids in syntheses of nature products and bioactive peptide inhibitors, see: (a) Lee, A. H. F.; Chan, A. S. C.; Li, T. *Tetrahedron* **2003**, *59*, 833. (b) Besant, B.; Bird, J.; Gaster, L. M.; Harper, G. P.; Hughes, I.; Karran, E. H.; Markwell, R. E.; Miles-Williams, A. J.; Smith, S. A. *J. Med. Chem.* **1993**, *36*, 4030.

(7) (a) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974. For the example of chiral-auxiliary-induced SMA of thiols to cinnamates, see: (b) Cousins, G.; Falashaw, A.; Hoberg, J. O. *Org. Biomol. Chem.* **2004**, *2*, 2272. For enzyme-promoted asymmetric SMA of thiols to (*E*)-4,4,4-trifluorocrotonate, see: (c) Kitazume, T.; Murata, K. *J. Fluorine Chem.* **1988**, *39*, 75. For cinchona alkaloids-promoted SMA of thiophenol to maleates, see: (d) Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, *14*, 363.

(8) Dong, X.-Q.; Fang, X.; Wang, C.-J. *Org. Lett.* **2011**, *13*, 4426. Only moderate enantioselectivity was observed for (*E*)-4,4,4-trifluorocrotonate.

(9) (a) Kano, T.; Shirozu, F.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 16068. (b) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2004**, *126*, 1352. (c) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

(10) For reviews on bifunctional organocatalysis, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (b) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496. (c) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418.

(11) (a) Wang, C.-J.; Zhang, Z.-H.; Dong, X.-Q.; Wu, X.-J. *Chem. Commun.* **2008**, 1431. (b) Zhang, Z.-H.; Dong, X.-Q.; Chen, D.; Wang, C.-J. *Chem.—Eur. J.* **2008**, *14*, 8780. (c) Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue, Z.-Y.; Teng, H.-L. *J. Am. Chem. Soc.* **2008**, *130*, 8606. (d) Dong, X.-Q.; Teng, H.-L.; Wang, C.-J. *Org. Lett.* **2009**, *11*, 1265. (e) Dong, X.-Q.; Fang, X.; Tao, H.-Y.; Zhou, X.; Wang, C.-J. *Adv. Synth. Catal.* **2012**, *354*, 1141.

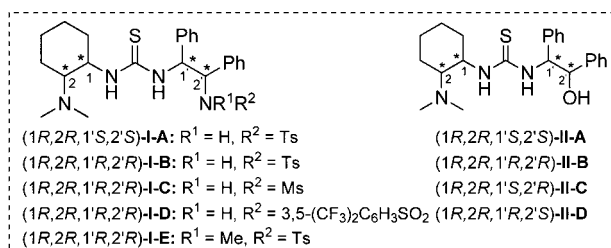
electron-withdrawing hexafluoroisopropyl moiety not only provided a superior level of reactivity but also afforded much higher enantioselectivity: the reaction finished smoothly in < 12 h leading to the desired adduct in almost quantitative yield with 82% ee (entry 4).

Encouraged by the promising results, fine-tunable bifunctional amine-thiourea catalysts **I** and **II** were subsequently screened, and the representative results are tabulated in Table 2. It was revealed that both reaction rate and enantioselectivity were significantly affected by the configuration matching of the two chiral units in the amine-thiourea catalysts and the acidity of the third

Table 2. Optimization of Catalytic Asymmetric SMA of Thiophenol **1a** with Hexafluoroisopropyl Cinnamate **5a**^a

entry	catal.	solvent	<i>t</i> (°C)	time (h)	yield (%) ^b	ee (%) ^c
1	I-A	CH ₂ Cl ₂	rt	24	92	–4
2	I-B	CH ₂ Cl ₂	rt	12	95	81
3	I-C	CH ₂ Cl ₂	rt	12	96	77
4	I-D	CH ₂ Cl ₂	rt	12	98	82
5	I-E	CH ₂ Cl ₂	rt	72	65	53
6	II-A	CH ₂ Cl ₂	rt	24	92	15
7	II-B	CH ₂ Cl ₂	rt	24	83	40
8	II-C	CH ₂ Cl ₂	rt	24	85	42
9	II-D	CH ₂ Cl ₂	rt	24	94	69
10	I-D	Ether	rt	22	94	76
11	I-D	PhMe	rt	9	95	95
12	I-D	MeCN	rt	4	88	14
13	I-D	MeOH	rt	4	86	7
14	I-D	PhMe	0	18	95	96
15 ^d	I-D	PhMe	0	24	96	96
16 ^e	I-D	PhMe	0	45	91	95

^a All reactions were carried out with 0.2 mmol of **5a** and 0.24 mmol of **1a** in 1 mL of solvent. ^b Isolated yield. ^c Ee was determined by HPLC analysis. ^d Catalyst loading: 5 mol %. ^e Catalyst loading: 1 mol %.



H-bonding donor (Table 2, entries 1–9). In general, a faster reaction rate was observed with organocatalysts **I**, which was ascribed to the additional stronger H-bonding donor contributed by the sulfonamide group, and catalyst **I-D** was revealed as the best in terms of enantioselectivity and reaction rate (entry 4). In contrast, the SMA reaction became sluggish and the adduct **6aa** was separated in only 65% yield even after 72 h when using methylated **I-E** as the

catalyst (entry 5). Other bifunctional acid–base catalysts were also tested in this transformation, producing the adduct with slightly lower enantioselectivities (see Supporting Information (SI) for more details). Subsequent evaluation of solvent effects improved the enantioselectivity to 95% when toluene was used as the solvent (entries 10–13). Up to 96% ee and a 95% yield were achieved when the reaction was carried out at 0 °C for 18 h (entry 14). Remarkably, the high yield and excellent enantioselectivity were maintained even when the SMA reaction was carried out with a 5 mol % catalyst loading (entry 15). A comparable result was still achieved even when the amine-thiourea catalyst loading was reduced to 1 mol % albeit at the expense of the reaction time (entry 16).

With the optimal reaction conditions in hand, we then turned our focus to the substrate scope and generality of this SMA reaction. In the presence of 5 mol % of catalyst **I-D**, the sulfa-Michael addition of different thiols to hexafluoroisopropyl cinnamate **5a** was examined, and the results are tabulated in Table 3. In general, a wide range of aryl thiols, bearing electron-neutral (entries 1 and 11),

Table 3. Substrate Scope of the Catalytic Asymmetric SMA of Thiols **1** with Hexafluoroisopropyl Cinnamate **5a**^a

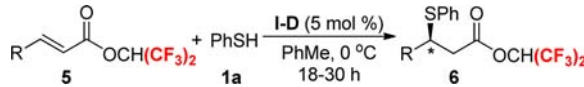
entry	R	product	yield (%) ^b	ee (%) ^c
1	Ph (1a)	6aa	96	96
2	<i>o</i> -Me-C ₆ H ₄ (1b)	6ab	93	97
3	<i>m</i> -Me-C ₆ H ₄ (1c)	6ac	92	95
4	<i>p</i> -Me-C ₆ H ₄ (1d)	6ad	97	97
5	<i>p</i> -MeO-C ₆ H ₄ (1e)	6ae	94	>99
6	<i>m</i> -F-C ₆ H ₄ (1f)	6af	91	94
7	<i>p</i> -F-C ₆ H ₄ (1g)	6ag	92	98
8	<i>p</i> -Cl-C ₆ H ₄ (1h)	6ah	95	96
9	<i>p</i> -CF ₃ -C ₆ H ₄ (1i)	6ai	92	93
10	<i>o</i> -NH ₂ -C ₆ H ₄ (1j)	6aj	93	98
11	2-naphthyl (1k)	6ak	92	98
12	2-thienyl (1l)	6al	90	90
13 ^d	PhCH ₂ (1m)	6am	82	93
14 ^d	<i>p</i> -MeO-C ₆ H ₄ CH ₂ (1n)	6an	86	93
15 ^d	<i>p</i> -Cl-C ₆ H ₄ CH ₂ (1o)	6ao	83	90
16 ^e	MeOOCCH ₂ (1p)	6ap	88	91

^a All reactions were carried out with 0.2 mmol of **5a** and 0.24 mmol of **1** in 1 mL of PhMe for 18–30 h. ^b Isolated yield. ^c Ee was determined by HPLC analysis. ^d For 48 h. ^e Carried out at –30 °C for 40 h.

–rich (entries 2–5 and 10), or –deficient groups (entries 6–9) on the phenyl ring, reacted smoothly with **5a** affording the

(12) (a) Krapcho, J.; Spitzmiller, E. R.; Turk, C. F. *J. Med. Chem.* **1963**, 6, 544. (b) Phippen, C. B. W.; McErlean, C. S. P. *Tetrahedron Lett.* **2011**, 52, 1490. The first asymmetric approach to (*R*)-thiazesim was reported through a complicated synthetic route consisting of seven steps promoted by enzyme; see: (c) Dike, S. Y.; Ner, D. H.; Kumar, A. *Bioorg. Med. Chem. Lett.* **1991**, 1, 383. For the latest example on the catalytic asymmetric synthesis of (*R*)-thiazesim, see ref 4f.

Table 4. Substrate Scope of the Catalytic Asymmetric SMA of Thiophenol **1a** with Various α,β -Unsaturated Hexafluoroisopropyl Esters **5**^a



entry	R	product	yield (%) ^b	ee (%) ^c
1	Ph (5a)	6aa	96	96
2	<i>o</i> -Me-C ₆ H ₄ (5b)	6ba	95	>99
3	<i>m</i> -Me-C ₆ H ₄ (5c)	6ca	94	95
4	<i>p</i> -Me-C ₆ H ₄ (5d)	6da	99	99
5	<i>p</i> -MeO-C ₆ H ₄ (5e)	6ea	93	96
6	<i>p</i> -Cl-C ₆ H ₄ (5f)	6fa	99	98
7	<i>p</i> -Br-C ₆ H ₄ (5g)	6ga	92	98
8	<i>m</i> -Br-C ₆ H ₄ (5h)	6ha	94	98
9	<i>p</i> -CF ₃ -C ₆ H ₄ (5i)	6ia	96	98
10	2-furyl (5j)	6ja	91	93
11	Me (5k)	6ka	90	96
12	<i>i</i> -Pr (5l)	6la	86	92
13	PhCH ₂ CH ₂ (5m)	6ma	92	96

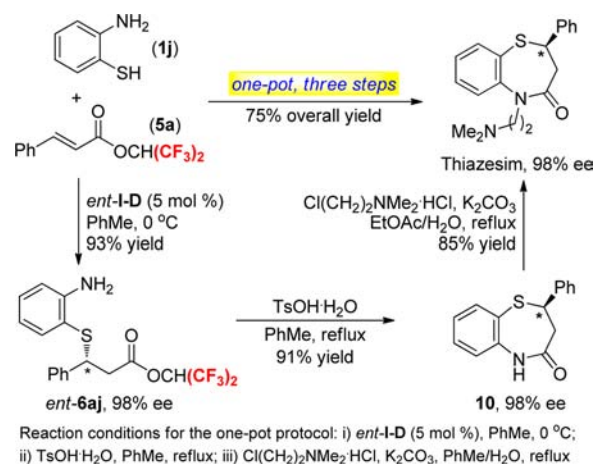
^a All reactions were carried out with 0.2 mmol of **5** and 0.24 mmol of **1a** in 1 mL of PhMe. ^b Isolated yield. ^c Determined by HPLC analysis.

Michael adducts in high yields (91–97%) with excellent enantioselectivities (93–>99% ee). The substitution pattern of the aromatic ring had almost no effect on the asymmetric induction. Notably, comparable results were also observed for the more sterically hindered *ortho*-methyl **1b** and *ortho*-amino substituted thiols **1j** in terms of reactivity and enantioselectivity (entries 2 and 10). Heteroaromatic thiophene-2-thiol **1l** was also tolerated in this SMA reaction and furnished the corresponding product **6al** with 90% ee (entry 12). Less reactive aliphatic thiols were further evaluated, and good yields and excellent enantioselectivities (90–93% ee) were achieved for all tested benzyl thiols albeit with an extended reaction time (entries 13–15). Noticeably, methyl thioglycolate **1p** was also tolerated in this SMA reaction leading to the product in 88% yield with 91% ee (entry 16).^{4j}

Next, the potential of this organocatalytic approach with respect to the electrophile is further investigated under the optimized reaction conditions. As shown in Table 4, all tested β -aryl α,β -unsaturated hexafluoroisopropyl esters have proven to be excellent Michael acceptors affording the expected adducts (**6aa**–**6ia**) in high yields and excellent enantioselectivities (Table 4, entries 1–9). The heteroaromatic furyl-substituted unsaturated ester **5j** proceeded well with **1a**, delivering the product **6ja** in 91% yield and 93% ee (entry 10). β -Alkyl α,β -unsaturated hexafluoroisopropyl esters also worked well in this catalytic system (entries 11–13). The consistently excellent enantioselectivities obtained with the sterically hindered β -isopropyl (**5l**) and β -aryl α,β -unsaturated fluorinated esters (**5a**–**5i**) are noteworthy, as the corresponding nonfluorinated esters were shown to be relatively challenging acceptors in the previous study employing a metal complex as the catalyst.^{7a}

To demonstrate the potential utility of this methodology, this organocatalyzed SMA reaction was applied to the concise synthesis of thiazesim, an antidepressant agent.¹² A concise route was designed to this target molecule that relies on the highly efficient *ent*-**I-D**-catalyzed asymmetric SMA of 2-aminothiophenol **1j** to hexafluoroisopropyl cinnamate **5a** (Scheme 2). Treatment of the adduct *ent*-**6aj** with TsOH monohydrate in toluene under reflux gave rise to benzothiazepinone **10** in 91% yield. Then, cyclic amide **10** was *N*-alkylated with 2-dimethylaminoethyl chloride hydrochloride leading to (*R*)-thiazesim in high yield with complete retention of stereochemistry.^{4f} Furthermore, a one-pot protocol for the above three-step transformation was also feasible affording enantiomerically enriched thiazesim in good overall yield with 98% ee (see SI for more synthetic transformations).

Scheme 2. Concise Synthesis of (*R*)-Thiazesim



In summary, we have developed an organocatalyzed asymmetric sulfa-Michael addition of thiols to a variety of hexafluoroisopropyl α,β -unsaturated esters for the first time. This organocatalytic system exhibited high reactivity, excellent enantioselectivity, and a broad substrate scope. Introduction of an electron-withdrawing hexafluoroisopropyl ester moiety was revealed to be the key point in enhancing the electrophilicity of α,β -unsaturated esters as SMA acceptors. The ready availability of unsaturated esters and the great importance of the chiral sulfur-containing compounds make the present methodology particularly interesting in synthetic organic chemistry, as demonstrated by the expedient synthesis of (*R*)-thiazesim in a one-pot protocol.

Acknowledgment. This work is supported by the 973 Program (2011CB808600), NSFC (20972117, 21172176), and NCET-10-0649, IRT1030.

Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.