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Squaramide—Tertiary Amine Catalyzed Asymmetric Cascade Sulfa-Michael/ Michael Addition via Dynamic Kinetic Resolution: Access to Highly Functionalized Chromans with Three Contiguous Stereocenters

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ABSTRACT



An efficient asymmetric cascade sulfa-Michael/Michael addition reaction catalyzed by a chiral bifunctional squaramide—tertiary amine catalyst has been developed. This organocatalytic cascade reaction provides easy access to highly functionalized chromans with three contiguous stereocenters, including one quaternary center. In addition, a novel cascade sulfa Michael/retro-sulfa-Michael/sulfa-Michael/Michael reaction process, involving dynamic kinetic resolution, is described.

Chroman is a fundamental heterocyclic skeleton found in a large family of natural products and medically synthetic molecules that exhibits a wide spectrum of significant biological activities.¹ In this context, great efforts have been devoted to the synthesis of chiral chromans, and numerous effective catalytic asymmetric approaches have been established.² Among these methods, organocatalytic cascade reactions were considered as a straightforward and powerful process to construct the chiral chroman framework. Several impressive examples for the synthesis of chiral chromans with multiple stereocenters were reported.³ In 2009, Wang's group reported a highly enantioselective cascade oxa-Michael/Michael reaction of 2-hydroxycinnamaldehydes with nitroalkenes catalyzed by a chiral diphenylprolinol TMS ether.^{3a} In 2010, Xiao and coworkers developed a chiral thiourea-catalyzed highly enantioselective sulfa-Michael/Michael cascade reaction of thiols with nitroalkene enoates.^{3b} Subsequently, they used anilines as donors to develop an efficient organocatalytic aza-Michael/Michael cascade reaction.^{3c} Very recently, Peng et al. reported a chiral thiourea-catalyzed highly

 ⁽a) Afantitis, A.; Melagraki, G.; Sarimveis, H.; Koutentis, P. A.; Markopoulos, J.; Igglessi-Markopoulou, O. *Bioorg. Med. Chem.* 2006, *14*, 6686. (b) Conti, C.; Monaco, L. P.; Desideri, N. *Bioorg. Med. Chem.* 2011, *19*, 7357. (c) Roll, D. M.; Manning, J. K.; Carter, G. T. J. *Antibiot.* 1998, *51*, 635. (d) Grisar, J. M.; Petty, M. A.; Bolkenius, F. N.; Dow, J.; Wagner, J.; Wagner, E. R.; Haegele, K. D.; Jong, W. D. J. Med. Chem. 1991, *34*, 257. (e) Kashman, Y.; Gustafson, K. R.; Fuller, R. W.; Cardellina, J. H., II; McMahon, J. B.; Currens, M. J.; Buckhiet, R. W., Jr.; Hughes, S. H.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* 1992, *35*, 273. (f) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* 2001, *57*, 1559.

⁽²⁾ For reviews, see: (a) Shi, Y.-L.; Shi, M. Org. Biomol. Chem. 2007, 5, 1499. (b) Wang, G. X.; Wang, N. X.; Tang, S.; Yu, J. L.; Tang, X. L. Prog. Chem. 2008, 20, 518. (c) Shen, H. C. Tetrahedron 2009, 65, 3931.

^{(3) (}a) Zu, L.; Zhang, S.; Xie, H.; Wang, W. Org. Lett. **2009**, *11*, 1627. (b) Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. Angew. Chem., Int. Ed. **2010**, *49*, 8379. (c) Wang, X.-F.; An, J.; Zhang, X.-X.; Tan, F.; Chen, J.-R.; Xiao, W.-J. Org. Lett. **2011**, *13*, 808. (d) Hou, W.; Zheng, B.; Chen, J.; Peng, Y. Org. Lett. **2012**, *14*, 2378.

asymmetric oxa-Michael/aza-Henry cascade reaction of salicylaldimines with nitroalkenes.^{3d} Despite a few successes, the development of efficient new cascade reactions or catalytic systems is still highly desirable.

In recent years, the emerging field of organocatalytic cascade reactions has attracted considerable attention, and great progress has been made.⁴ Organocatalysts for cascade reactions mainly include proline and its derivatives. cinchona alkaloid-based primary amines, thioureas, and phosphoric acids. Squaramides are a class of good hydrogen-bonding organocatalysts and have been increasingly utilized in organocatalysis.^{5,6} Nevertheless, they are still rarely employed in cascade reactions.⁷ Recently, our group also reported some asymmetric Michael addition reactions catalyzed by squaramides.⁸ In addition, a large number of methods on asymmetric Michael addition of nitroalkenes have been reported.9 Herein, we document an efficient squaramide-catalyzed asymmetric cascade sulfa-Michael/ Michael addition of thiosalicylates with nitroalkene enoates for the construction of highly functionalized chromans containing three contiguous stereocenters.

We commenced our study with methyl thiosalicylate 1a and nitroalkene enoate 2a as the model substrates. The model reaction was performed in the presence of 5 mol % of squaramide catalyst I (Figure 1) in CH₂Cl₂ at 15 °C for

(5) For reviews of squaramides, see: (a) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330. (b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem.—Eur. J.* **2011**, *17*, 6890.

(6) For selected examples of asymmetric reactions using squaramides, see: (a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. J. Am. Chem. Soc. 2008, 130, 14416. (b) Zhu, Y.; Malerich, J. P.; Rawal, V. H. Angew. Chem., Int. Ed. 2010, 49, 153. (c) Xu, D. Q.; Wang, Y.-F.; Zhang, W.; Luo, S.-P.; Zhong, A.-G.; Xia, A.-B.; Xu, Z.-Y. Chem.—Eur. J. 2010, 16, 4177. (d) Qian, Y.; Ma, G.; Lv, A.; Zhu, H.-L.; Zhao, J.; Rawal, V. H. Chem. Commun. 2010, 46, 3004. (e) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. Org. Lett. 2010, 12, 2028. (f) Pansare, S. V.; Paul, E. K. Chem. Commun. 2011, 47, 1027. (g) Min, C.; Han, X.; Liao, Z. Q.; Wu, X. F.; Zhou, H.-B.; Dong, C. Adv. Synth. Catal. 2011, 353, 2715. (h) Bae, H. Y.; Somg, C. E. Adv. Synth. Catal. 2011, 353, 3196. (i) Wang, C.; Yang, X.; Loh, C. C. J.; Raabe, G.; Enders, D. Chem.—Eur. J. 2012, 18, 11531. (j) Noole, A.; Jaerving, I.; Werner, F.; Lopp, M.; Malkov, A.; Kanger, T. Org. Lett. 2012, 14, 4922.

(7) For examples of squaramide-catalyzed asymmetric cascade reactions, see: (a) Wang, X.; Yao, W.; Yao, Z.; Ma, C. J. Org. Chem. 2012, 77, 2959. (b) Ling, J.-B.; Su, Y.; Zhu, H.-L.; Wang, G.-Y.; Xu, P.-F. Org. Lett. 2012, 14, 1090. (c) Sun, W.; Zhu, G.; Wu, C.; Hong, L.; Wang, R. Chem.—Eur. J. 2012, 18, 6737. (d) Duan, S.-W.; Li, Y.; Liu, Y.-Y.; Zou, Y.-Q.; Shi, D.-Q.; Xiao, W.-J. Chem. Commun. 2012, 48, 5160.

(8) (a) Yang, W.; Du, D.-M. Org. Lett. **2010**, *12*, 5450. (b) Yang, W.; Du, D.-M. Adv. Synth. Catal. **2011**, 353, 1241. (c) Yang, W.; Du, D.-M. Chem. Commun. **2011**, 47, 12706. (d) Yang, W.; Jia, Y.; Du, D.-M. Org. Biomol. Chem. **2012**, *10*, 332. (e) Yang, W.; Du, D.-M. Org. Biomol. Chem. **2012**, *10*, 6876. (f) Yang, W.; Wang, J. S.; Du, D.-M. Tetrahedron: Asymmetry **2012**, *23*, 972.

(9) For reviews, see: (a) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* 2007, *18*, 299. (b) Enders, D.; Lüttgen, K.; Narine, A. A. *Synthesis* 2007, 959. Some recent examples: (c) Ding, M.; Zhou, F.; Liu, Y.-L.; Wang, C.-H.; Zhao, X.-L.; Zhou, J. *Chem. Sci.* 2011, *2*, 2035. (d) Dong, X.-Q.; Fang, X.; Wang, C.-J. *Org. Lett.* 2011, *13*, 4426. (e) Pei, Q.-L.; Sun, H.-W.; Wu, Z.-J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* 2011, *76*, 7849. (f) Ding, M.; Zhou, F.; Qian, Z.-Q.; Zhou, J. *Org. Biomol. Chem.* 2010, *8*, 2912. (g) Hui, Y.; Jiang, J.; Wang, W.; Chen, W.; Cai, Y.; Lin, L.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* 2010, *49*, 4290.



Figure 1. Squaramide catalysts.

12 h. Pleasingly, the asymmetric cascade sulfa-Michael/Michael addition proceeded smoothly to afford the desired chroman 3aa in 83% yield with good diastereoselectivity and enantioselectivity (88:12 dr and 87% ee) (Table1, entry 1). However, the sulfa-Michael adduct 4aa was also obtained in 10% yield. After trials, temperature was found to benefit the cascade reaction. The reaction was complete at 40 °C in 4 h and only afforded the corresponding chroman 3aa in excellent yield with almost the same good diastereoselectivity and enantioselectivity (Table 1, entry 2). Encouraged by the initial result, we then investigated the effect of solvent and temperature for the optimal reaction conditions. The results are presented in Table 1. The solvent optimization disclosed that MeCN was the best reaction medium (Table 1, entry 6). Variation of the solvents had little effect on the reaction. The solvents such as ClCH₂CH₂Cl, CHCl₃, and toluene gave the comparable results as CH₂Cl₂, and the solvents THF and *i*-PrOH provided lower enantioselectivities (78% ee and 73% ee, respectively) (Table 1, entries 3-5, 7, and 8). When reactions were performed at higher temperature (60 or 80 °C), high diastereoselectivity and enantioselectivity were maintained (Table 1, entries 9 and 10). Finally, we chose 60 °C as the optimal reaction temperature.

With the optimal reaction conditions in hand, we screened a small library of squaramide catalysts I-X (Figure 1). The results are summarized in Table 2. Squaramide II with 4-CF₃ on the aromatic ring gave slightly lower diastereoselectivity and enantioselectivity (88:12 dr, 86% ee) (Table 2, entry 2). Squaramides III and IV derived from quinidine afforded the desired adducts with similar results, but with opposite configuration (Table 2, entries 3 and 4). We then turned our attention to these squaramides V-IX derived from chiral 1,2-diaminocyclohexane (Table 2, entries 5-9). Among them, squaramides VII and IX gave higher diastereoselectivity and enantioselectivity, but squaramide IX provided the adduct 3aa in lower yield because of the formation of sulfa-Michael adduct 4aa. C2-symmetric quinine-derived squaramide X were also examined, and lower diastereoselectivity and enantioselectivity was obtained (Table 2, entry 10). Therefore, squaramide VII was selected as the best catalyst. Subsequently, the effect of catalyst loading was investigated. The catalyst loading affected reaction rate, but rarely did the

⁽⁴⁾ For reviews of organocatalytic cascade reactions, see: (a) Enders,
D.; Grondal, C.; Huttl, M. R. Angew. Chem., Int. Ed. 2007, 46, 1570.
(b) Yu, X.; Wang, W. Org. Biomol. Chem. 2008, 6, 2037. (c) Alba, A.-N.;
Companyo, X.; Viciano, M.; Rios, R. Curr. Org. Chem. 2009, 13, 1432.
(d) Grondal, C.; Jeanty, M.; Enders, D. Nature Chem. 2010, 2, 167.
(e) Pellissier, H. Adv. Synth. Catal. 2012, 354, 237.

Table 1. Optimization of Reaction Conditions^a



entr	y solvent	loading (mol %)	temp (°C)	time (h)	yield ^b (%)	dr^c	$\mathrm{ee}^{c,d}$ (%)
1	CH_2Cl_2	5	15	12	83	88:12	87
2	CH_2Cl_2	5	40	4	97	89:11	88
3	ClCH ₂ CH ₂ Cl	5	40	4	93	89:11	85
4	$CHCl_3$	5	40	4	97	89:11	89
5	PhMe	5	40	4	96	87:13	88
6	MeCN	5	40	4	96	93:7	88
7	THF	5	40	4	90	88:12	78
8	iPrOH	5	40	4	84	93:7	73
9	MeCN	5	60	2	96	93:7	89
10	MeCN	5	80	1	95	92:8	88

^{*a*} Reactions were carried out with **1a** (0.12 mmol) and **2a** (0.1 mmol) in solvent (0.5 mL). ^{*b*} Isolated yield of **3aa**. ^{*c*} Determined by chiral HPLC analysis. ^{*d*} Enantiomeric excess of the major diastereomer.

diastereoselectivity and enantioselectivity (Table 2, entries 11-13). Considering the yield and reaction time, 1 mol % of catalyst loading was our appropriate choice.



^{*a*} Reactions were carried out with **1a** (0.12 mmol) and **2a** (0.1 mmol) in MeCN (0.5 mL) at 60 °C for 2 h. ^{*b*} Isolated yield. ^{*c*} Determined by chiral HPLC analysis. ^{*d*} Enantiomeric excess of the major diastereomer. ^{*e*} 10 mol % of **VII** for 2 h. ^{*f*} 1 mol % of **VII** for 5 h. ^{*g*} 0.5 mol % of **VII** for 8 h. ^{*b*} Opposite enantiomer.

Having established the optimal reaction conditions, we explored the scope of the squaramide-catalyzed asymmetric cascade sulfa-Michael/Michael addition reaction. The results are shown in Table 3. First, thiosalicylates **1b** and **1c**

with different R^1 substitution were tested, and the corresponding adducts were obtained in excellent yields with high diastereoselectivities and enantioselectivities (95:5 dr, 90% ee) (Table 3, entries 2 and 3). The results show that R^1 substitution has no effect on the stereoselectivity. Maybe it is because R¹ substitution is far from asymmetric induction position. Then an array of nitroalkene enoates 2b-i derived from various salicylaldehydes reacted smoothly with methyl thiosalicylates **1a** to afford the corresponding adducts in high vields with good to high diastereoselectivities and enantioselectivities (Table 3, entries 4-12). Among them, 3,5-dichloro- and 3,5-dibromosalicylaldehyde-derived nitroalkene enoates 2f and 2g gave lower diastereoselectivities and enantioselectivities, and nitroalkene enoate 2h exhibited lower reactivity. Further substrate scope was investigated. When thiophenol 1d was employed, the desired adduct 3da was obtained in moderate yield (60%) with high diastereoselectivity and good enantioselectivity (>95:5 dr, 87% ee) (see the Supporting Information). A linear aliphatic nitroalkene enoate ((2E,7E)-ethyl 8-nitronona-2,7-dienoate) was examined, but no cascade process was observed. The

Table 3. Squaramide-Catalyzed Asymmetric Cascade Sulfa-Michael/Michael Addition of Thiosalicylates 1 to NitroalkeneEnoates 2^{a}

SH CO:	2R ¹		CO ₂ Et	1 mol % MeCN, 60 °	VII (2E
		_				51		
entry	I R ¹	2 R ²	R ³	product	yield $(\%)^b$	dr^c	ee (%) ^d	
1	Me	Н	Me	3aa	96	95:5	91	
2	Et	н	Me	3ba	96	95:5	90	
3	<i>n</i> -Bu	Н	Me	3ca	95	95:5	90	
4	Me	2-OMe	Me	3ab	98	95:5	92	
5	Me	2-OEt	Me	3ac	94	93:7	94	
6	Me	4-Cl	Me	3ad	96	9:1	89	
7	Me	4-Br	Me	3ae	97	9:1	90	
8	Me	2,4-Cl ₂	Me	3af	93	5:1	84	
9	Me	2,4-Br ₂	Me	3ag	92	5:1	83	
10^{e}	Me		O ₂ Et	3ah	88	90:10	83	
11	Me	Н	Et	3ai	92	95:5	95	
12	Me	2-OEt	Et	3aj	93	9:1	89	

^{*a*} Reactions were carried out with **1** (0.24 mmol) and **2** (0.2 mmol) in MeCN (1.0 mL) at 60 °C. ^{*b*} Isolated yield. ^{*c*} Determined by chiral HPLC analysis or ¹H NMR. ^{*d*} Enantiomeric excess of the major diastereomer by chiral HPLC analysis. ^{*e*} Reaction was performed for 32 h.

absolute configuration of **3ae** was determined to be 2*S*,3*S*,4*S* by X-ray analysis (Figure S1, Supporting Information), and those of other adducts were assigned by analogy.

The sulfa-Michael adduct **4aa** observed in our initial investigation is a reactive intermediate, which offers us a

Table 4. Study on the Cascade Reaction Pathway^a



entry	reactant	loading (mol %)	time (h)	yield ^b (%)	$d\mathbf{r}^c$	$\mathrm{ee}^{c,d}$ (%)
1	anti- 4aa (49% ee)	2	36	92	95:5	90
2	<i>syn-</i> 4aa (93% ee)	10	60	92	94:6	90
3	rac-anti- 4aa	2	36	93	94:6	91
4	rac-syn- 4aa	10	60	96	95:5	91

^{*a*} Reactions were carried out with **4aa** (0.1 mmol) in MeCN (1.0 mL) at 60 °C. ^{*b*} Isolated yield. ^{*c*} Determined by chiral HPLC analysis. ^{*d*} Enantiomeric excess of the major diastereomer.

good opportunity to realize the cascade reaction pathway. The adducts anti-4aa (49% ee) and syn-4aa (93% ee) were prepared with very different enantioselectivities in the presence of 2 mol % of VII at -20 °C, but they were converted to the desired chroman 3aa with almost the same results (Table 4, entries 1 and 2). The results were the same as that of the cascade reaction of methyl thiosalicylate 1a and nitroalkene enoate 2a. The unexpected observation signifies that the transformation from 4aa to 3aa is not by a direct Michael addition but may be by a retro-sulfa-Michael/sulfa-Michael/Michael process. To verify the hypothesis, racemic anti-4aa and syn-4aa were treated under the same reaction conditions. As expected, similar results were achieved (Table 4, entries 3 and 4). Based on the observed results and relative reports, we proposed a sulfa-Michael/retro-sulfa-Michael/sulfa-Michael/Michael process, involving dynamic kinetic resolution, for the asymmetric cascade reaction (Scheme 1).¹⁰

As shown in Scheme 2, to highlight the synthetic value of this methodology, the gram-scale preparation of **3aa** and its transformation were performed. The model cascade reaction was readily gram-scaled without significant changes in yield, diastereoselectivity, or enantioselectivity. The chroman **3aa** underwent reduction and transesterification to afford **5**, which was easily converted into γ -lactam **6** by heating in argon. The chroman **3aa** was also transformed into the corresponding 2*H*-chromenes (**7** or **8**) by eliminating a nitrous acid, but with complete loss of enantioselectivity. The result indicated the transformation first underwent the formation of 4*H*-chromenes as intermediates.

In conclusion, we have developed an efficient squaramidecatalyzed asymmetric cascade sulfa-Michael/Michael addition for the synthesis of chiral chromans. The cascade Scheme 1. Proposed Cascade Reaction Pathway



Scheme 2. Gram-Scale Preparation of 3aa and Its Transformation



reactions with 1 mol % of squaramide **VII** proceeded well to furnish the corresponding chromans in high yields with high diastereoselectivity and enantioselectivity (up to 95:5 dr, 95% ee). This approach provides easy access to highly functionalized chromans with three contiguous stereocenters, including one quaternary center. In addition, a novel cascade reaction pathway (sulfa-Michael/retro-sulfa-Michael/sulfa-Michael/Michael process), involving dynamic kinetic resolution, is described. Futher studies on asymmetric cascade reactions catalyzed by squaramides are ongoing in our laboratory.

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Supporting Information Available. Experimental procedures and characterizations, copies of ¹H NMR and ¹³C NMR of new compounds, X-ray crystal structure of **3ae** (CIF), and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

⁽¹⁰⁾ Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. Angew. Chem., Int. Ed. 2008, 47, 4177.

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