## Enantioselective Protonation in the Sulfa-Michael Addition Using Chiral Squaramides as Hydrogen-Bonding Organocatalysts

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**Abstract:** An enantioselective protonation of transient enolate generated in sulfa-Michael addition was investigated. Various  $\alpha$ -substituted acrylic derivatives and thiols were examined as substrates.  $\alpha$ -Benzyl acrylimide gave the best results in terms of chemical yield and enantioselectivity (up to 93% yield and 92% ee)

**Key words:** asymmetric protonation, enantioselective catalysis, squaramide, hydrogen bonding

Enantioselective protonation of prochiral enolates has become one of the most intensively studied reactions in the field of asymmetric catalysis over the past several years. This reaction provides an efficient way to access a wide range of optically active carbonyl compounds that possess a tertiary stereogenic carbon at the  $\alpha$ -position.<sup>1</sup> The majority of such reactions have been focused on the use of isolated enolate precursors, which were mainly derived from α-substituted cyclic ketones.<sup>2</sup> An attractive and challenging variant of this type of process is the asymmetric conjugated addition of  $\alpha$ -substituted acrylic derivatives via enantioselective protonation. To date, only chiral metal complexes<sup>3</sup> and strong basic guanidine derivatives<sup>4</sup> have proven to be efficient catalytic systems for this asymmetric transformation. Therefore, the development of conceptually different catalytic alternatives is still of great interest.

The use of chiral bifunctional catalysts for the synthesis of optically active compounds is popular in contemporary organic chemistry.<sup>5</sup> Simultaneous activation of both nucleophilic and electrophilic substrates within an asymmetric space is proven to be a potent manner to improve the reactivity as well as the stereodiscrimination.<sup>6</sup> However, the application of bifunctional catalysts in tandem conjugated addition-protonation reactions has been less explored.<sup>7</sup> In our previous studies, we have documented that the chiral squaramide 1 (Figure 1) can act as an effective bifunctional organocatalyst on enantioselective conjugated additions of thiols to  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>8a,b</sup> As an extending research, we describe here the development of the hydrogen-bonding-controlled asymmetric enolate protonation involving thiols and α-substituted acrylimides as substrates. This process enables the

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Figure 1 Structures of chiral squaramides 1–3

synthesis of  $\alpha$ -benzyl- $\beta$ -sulfureted propionic acid derivatives with a high level of enantioselectivity.

Initially,  $\alpha$ -methyl acrylimides **4a–c** bearing various achiral templates (*N*-oxazolinone, *N*-carbamate, *N*-benzoyl) were examined by using our previously established conditions:<sup>8b</sup> benzyl thiol **5a** (0.3 mmol, 1.5 equiv) was added to a solution of imides **4** (0.2 mmol) and **1** (2 mol%) in dichloromethane. All reactions proceeded smoothly at room temperature and were completed within 48 hours, giving the corresponding adducts in good yields with moderate enantioselectivities (Table 1, entries 1–3). Substrate **4c** showed excellent reactivity and relatively high selectivity.

Next, we tested other squaramide catalysts. Rawal's catalyst  $2^{8d}$  and Song's  $C_2$ -symmetric squaramide  $3^{8h}$  both gave lower enantioselectivities (Table 1, entries 4 and 5). Therefore, we chose squaramide 1 as most promising catalyst for further optimization of reaction conditions. Solvent survey revealed that nonpolar solvents are suitable for this transformation. Moreover, we found that the presence of water in the model reaction showed a significant drop in selectivity (data not shown). In contrast, the adduct was formed with 79% ee when 4 Å molecular sieves were added to the reaction system (Table 1, entry 6). We speculated that water as a type of proton source could participate in the proton sources as additives in the model

	Z + BnSH	catal addit	yst (2 mol%) ive, CH <sub>2</sub> Cl <sub>2</sub>	BnS	* Z	
4a-	c 5a			6	ia–c	
Z =	, s, N a	, <sup>55</sup> , N H	OMe D	م محمد المحمد محمد المحمد		
Entry	Substrate	Catalyst	Additive		Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	4a	1	-		86	55
2	4b	1	-		82	50
3	4c	1	-		93	60
4	4c	2	_		89	-43 <sup>d</sup>
5	4c	3	_		81	31
6	4c	1	4 Å MS		92	79
7	4c	1	4 Å MS, j	phenol	92	70
8	4c	1	4 Å MS,	1-naphthol	91	60
9	4c	1	4 Å MS, .	AcOH	67	-60 <sup>d</sup>
10	4c	1	4 Å MS, 1	PhCOOH	45	-53 <sup>d</sup>
11 <sup>e</sup>	4c	1	4 Å MS		91	83

 
 Table 1
 Template Identification and Optimization of Reaction Conditions<sup>a</sup>

<sup>a</sup> Unless otherwise noted, the reactions were carried out with 0.2 mmol of **4** and 0.3 mmol of **5a** in 1 mL of CH<sub>2</sub>Cl<sub>2</sub> under nitrogen atmosphere.

<sup>b</sup> Isolated yields.

<sup>c</sup> Determined by HPLC analysis using a Chiracel OD-H or AD-H column.

<sup>d</sup> Reversed enantioselectivity was obtained.

<sup>e</sup> The reaction was conducted at -40 °C

reaction. Addition of phenols in a catalytic amount provided products with lower enantioselectivities (Table 1, entries 7 and 8). The presence of acetic or benzoic acid slowed down the reaction rates and gave reversed enantioselectivities (Table 1, entries 9 and 10). These results indicated that protonating additives should be disfavored for this asymmetric transformation. Finally, we conducted the model reaction at lower temperature in order to improve the enantioselectivity. It was found that the ee value was elevated to 83% at -40 °C (Table 1, entry 11).

With the optimized conditions, we embarked on the investigation of the generality of the reaction with respect to  $\alpha$ substituent on the acrylimide acceptor. The results are presented in Table 2. As noted earlier, the reaction of  $\alpha$ methyl acrylimide **4c** with benzyl thiol (**5a**) gave the corresponding product in high yield with 83% ee (Table 2, entry 1). But the reaction involving  $\alpha$ -allyl acrylimide as substrate became very slow under these conditions. Only trace product was observed even in extended reaction time at room temperature (Table 2, entry 2). The highest enanTable 2 Asymmetric Addition of 5a to 4c-h with Catalyst 1a



Entry	Imide	Time (h)	Temp (°C)	Product	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	4c	48	-40	6c	91	83
2	4d	120	25	6d	trace	_
3	<b>4e</b>	24	-40	6e	93	92 <sup>d</sup>
4	4f	24	-40	6f	95	74
5	4g	60	-40	6g	91	27
6 <sup>e</sup>	4h	48	-40	6h	91	46

<sup>a</sup> Unless otherwise noted, the reactions were carried out with 0.2 mmol of **4** and 0.3 mmol of **5a** in 1 mL of  $CH_2Cl_2$  under nitrogen atmosphere.

<sup>b</sup> Isolated yields.

<sup>c</sup> Determined by HPLC analysis using a Chiracel OD-H or AD-H column.

<sup>d</sup> The absolute configuration of **6f** was assigned to be *S* by the rotation after conversion to acid.<sup>9,</sup>

<sup>e</sup> *p*-Methoxybenzyl thiol was used as nucleophile.

tioselectivity of 92% ee was obtained with  $\alpha$ -benzyl-substituted acceptor (Table 2, entry 3). Substrate containing functionalized  $\alpha$ -substituent furnished the product with lower enantiomeric excess (Table 2, entry 4). On the other hand, the piperonyl and aryl substitutions of the substrates gave poor to moderate selectivities, albeit with good reactivity (Table 2, entries 5 and 6).

These results indicated that the stereochemistry of the catalytic Michael protonation process might strongly dependent on  $\alpha$ -substituent on the acrylimide acceptor. Therefore,  $\alpha$ -benzyl acrylimide **4e** was chosen as a competent acceptor to evaluate a variety of thiols under the optimal reaction conditions. High enantioselectivities were achieved for simple thiols and benzyl thiols with electrondonating substituents (Table 3, entries 1–4). The reaction involving p-chlorobenzyl thiol furnished the desired product in 93% yield and slightly lower enantioselectivity (Table 3, entry 5). In the cases of thiophenol and thioacetic acid, the adducts were obtained with poor enantioselectivities in the same conditions (Table 3, entries 6 and 7). We considered that excess protonic reagents existing in the reactions could play a role of proton source to influence the stereodefining step. Therefore, a new reaction protocol was devised, where thiophenol or thioacetic acid are introduced slowly to a mixture of catalyst and 4e via a syringe pump (over 12 h). To our delight, the new protocol leads to significant enhancement of enantioselectivities in the reactions using thiophenol or thioacetic acid as nucleophiles (Table 3, entries 8 and 9).

 Table 3
 Asymmetric Addition of 5b-h to 4e with Catalyst 1<sup>a</sup>



Entry	Thiol	Time (h)	Product	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	5b	72	6i	76	89
2	5c	72	6j	70	89
3	5d	40	6k	92	87
4	5e	40	61	89	90
5	5f	24	6m	93	81
6	5g	24	6n	90	13
7	5h	24	60	94	46
8 <sup>d</sup>	5g	24	6n	91	37
9 <sup>d</sup>	5h	24	60	92	73

<sup>a</sup> Unless otherwise indicated, the reactions were carried out with 0.2 mmol of **4e** and 0.3 mmol of **5** in 1 mL of  $CH_2Cl_2$  under nitrogen atmosphere.

<sup>b</sup> Isolated yields.

° Determined by HPLC analysis using a Chiracel OD-H or AD-H column.

<sup>d</sup> Compound **5g** or **5h** was added via syringe pump over 12 h and the reactions were carried out at r.t.

In summary, we have demonstrated that chiral squaramide **1** worked well as a bifunctional organocatalyst in the tandem Michael–protonation reaction of  $\alpha$ -substituted acrylimides and alkyl thiols and furnished the corresponding products with moderate to good enantioselectivities. These results significantly expanded the scope of the asymmetric catalysis of bifunctional squaramide. Further investigations to improve the enantioselectivity by using assembled organocatalyst are ongoing in our laboratory.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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