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A Bifunctional *Cinchona* Alkaloid-Squaramide Catalyst for the Highly Enantioselective Conjugate Addition of Thiols to *trans*-Chalcones

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Abstract: A chiral squaramide catalysts-promoted asymmetric sulfa-Michael conjugated addition of thiols to *trans*-chalcones is presented. Moderate to excellent yields and high enantioselectivities (up to 99% *ee*) were achieved under mild conditions.

Keywords: asymmetric catalysis; bifunctional organocatalyst; squaramides; sulfa-Michael addition

The development of efficient catalytic methodologies for the stereoselective preparation of chiral sulfur-containing compounds is an important synthetic target.[1] The enantiopure sulfides are a key structural feature of several classes of pharmaceuticals and natural products and are extremely versatile building blocks that can undergo synthetically useful transformations.[2] The catalytic asymmetric sulfa-Michael addition (SMA) of thiols to electron-deficient olefins represents a straightforward and versatile approach toward such valuable optically active sulfur compounds.[3] Considerable effort has been directed to the development of the Lewis acid-promoted addition of strong nucleophilic aryl thiols as Michael donors to α,β-unsaturated carbonyl compounds through the use of various types of chiral ligands.[4] The direct organocatalytic asymmetric SMA to Michael acceptors using aryl and alkyl thiols as the sulfur-centered nucleophiles has attracted considerable attention due to their simple manipulation and high atom economy, and successful results have been documented by several research groups.[5,6] However, the Michael acceptors used in these sulfa-Michael additions generally have been limited to nitroolefins, enones, α,β-unsaturated aldehydes and carboxylic acid derivatives. To the best of our knowledge, there are only a few examples of organocatalytic SMAs involving *trans*-chalcones as Michael acceptors.[7] Nevertheless, these catalysis systems still have certain limitations such as poor enantioselectivity[7b–d], lower substrate scope, low reaction temperature, relatively high catalyst loading (~20 mol%)[7a]. Thus, the development of general and highly enantioselective SMAs of thiols to *trans*-chalcones under mild reaction conditions still remains an important and challenging goal in synthetic organic chemistry.

Catalysis employing hydrogen bonding for substrate activation has been proved to be an effective and versatile strategy in facilitating a variety of organic transformations.[8] Bifunctional *Cinchona* alkaloid derivatives (**1** and **2**) possessing various hydrogen-bonding

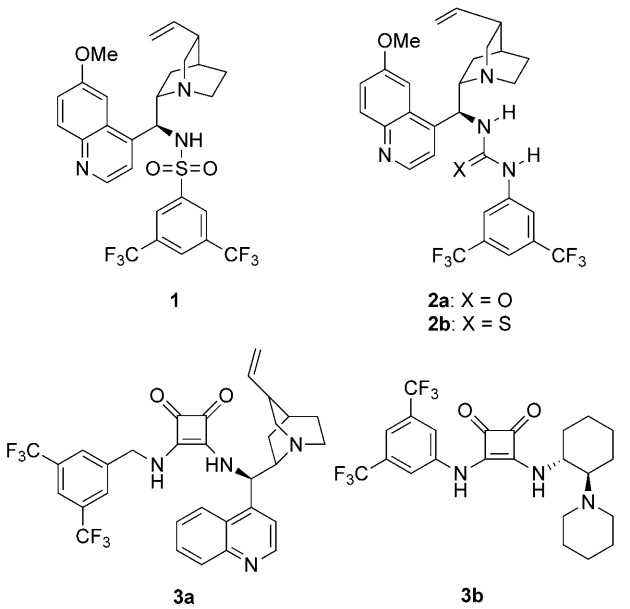


Figure 1. Structures of bifunctional organocatalysts **1**–**3**.

moieties, such as sulfonamide, urea, and thiourea, etc., have been widely used in a diverse range of asymmetric organic reactions in recent years (Figure 1).[9] Chiral squaramide catalysts (**3a**, **b**), developed recently in Rawal's group by incorporating the squaramide moiety as a powerful hydrogen bond donor in different chiral scaffolds, have been identified as a new family of efficient and versatile bifunctional organocatalysts for asymmetric chemical transformations.[10] Soon after that, Song and Xu also reported the use of chiral squaramide catalysts in the dynamic kinetic resolution of racemic azlactones[11a] and enantioselective conjugated addition of 4-hydroxypyrone to β,γ-unsaturated α-keto esters,[11b] respectively. Herein, we describe our successful applications of *Cinchona* alkaloid-squaramide catalysts to the highly enantioselective Michael addition of thiols to *trans*-chalcones at room temperature.

Squaramide-substituted *Cinchona* alkaloid derivatives **4a–4f** (Figure 2) could be prepared simply by condensation of 9-amino(9-dehydroxy)epiquinine with 3-aromatic amino-substituted squarates, which were accessed *via* amination of commercially available dimethyl squarate.

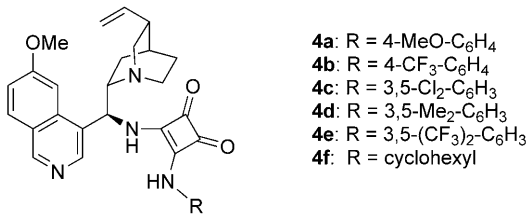
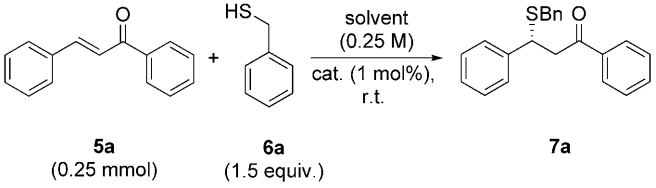


Figure 2. Structures of new squaramide-substituted *Cinchona* alkaloid catalysts **4a–4f**.

The addition of benzyl thiol to *trans*-chalcone was conducted as a model reaction to determine the catalytic activity of the squaramide catalysts **4a–4f** (Table 1). We first examined the catalysts **4a** and **4b**, which had different substituents on the *para* position of the aromatic rings. Electron-donating groups on the aryl group prolonged the reaction time, but did not affect the stereochemistry. Of the *meta* position-substituted catalysts **4c**–**4e**, **4d** and **4e** showed marked superiority on enantioselectivity. A value of 92% *ee* was obtained with catalyst **4e**, possessing two CF_3 groups on the aromatic ring. This outcome implied that steric hindrance of the aromatic rings and acidity of the squaramide N–H groups were related directly to the stereoselectivity and chemical yield. The unsatisfactory result with cyclohexyl-substituted squaramide catalyst **4f** indicated the irreplaceable role of the aromatic group in the enhancement of catalyst activity and selectivity.

Table 1. Asymmetric conjugate addition of benzyl thiol **6a** to *trans*-chalcone **5a** with squaramide catalysts **4a–4f**.[a]



5a (0.25 mmol) **6a** (1.5 equiv.) **7a**

Entry	Solvent	Catalyst	*t* [h][b]	Yield [%][c]	*ee* [%][d]
1	CH_2Cl_2	**4a**	6	81	63
2	CH_2Cl_2	**4b**	3	91	63
3	CH_2Cl_2	**4c**	3	90	62
4	CH_2Cl_2	**4d**	10	81	84
5	CH_2Cl_2	**4e**	3	98	92
6	CH_2Cl_2	**4f**	12	48	33
7	$CHCl_3$	**4e**	3	98	94
8	THF	**4e**	5	92	90
9	Et_2O	**4e**	5	91	94
10	toluene	**4e**	3	97	96
11	MeCN	**4e**	3	93	33
12	MeOH	**4e**	3	95	10

[a] The reaction between *trans*-chalcone (0.25 mmol) and benzyl thiol (0.375 mmol) was carried out in 1 mL solvent in the presence of 1 mol% catalyst at room temperature.
[b] Reaction time.
[c] Yield of isolated product.
[d] Determined by HPLC analysis using a Chiracel OJ-H column.

Having identified the squaramide catalyst **4e** as the strongest candidate of the library, we undertook a screen of solvents in the Michael reaction of benzyl thiol and *trans*-chalcone at room temperature. Consistent with our speculation, non-polar solvents were more suitable for H-bonding catalysis reactions (Table 1, entries 8–12). Reaction in MeCN led to a significant drop in enantioselectivity, albeit without loss of chemical yield (entry 11). But in the case of methanol (entry 12), the enantioselectivity decreased to 10% *ee*, probably because of competition for the hydrogen bonding activity of the solvent with the catalyst. Excellent reaction rate and enantiocontrol were obtained when toluene was used as solvent. The absolute configuration of the C-3 position of **7a** was determined to be *R* by comparison with the reported optical rotation data.[7a,b]

Under these optimized experimental conditions, a range of thiols was surveyed (Table 2). A less satisfactory level of stereoselectivity was observed with an aromatic thiol probably due to its stronger proton acidity (entry 1). Substituented benzyl thiols and furfuryl thiol furnished the corresponding Michael adducts in excellent enantioselectivites (up to 99% *ee*) and yields (entries 2–4). The reactions with simple alkyl thiols were relatively slow, and the *ee* dropped down

Table 2. Asymmetric conjugate addition of various thiols to *trans*-chalcones with catalyst **4e**.[a]

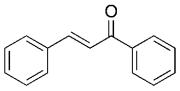
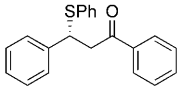
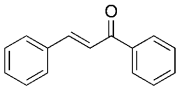
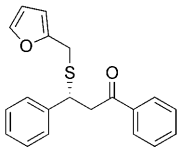
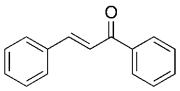
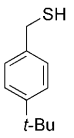
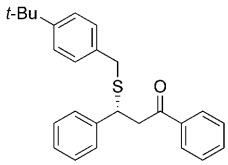
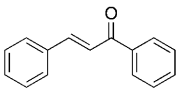
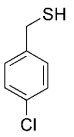
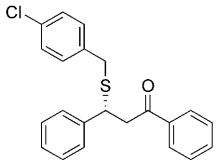
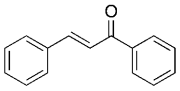
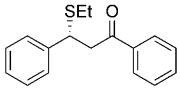
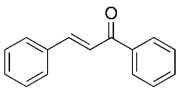
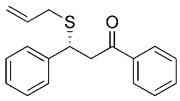
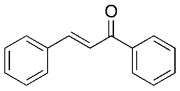
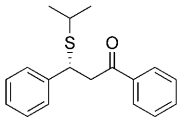
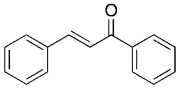
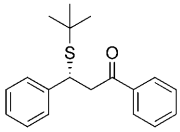
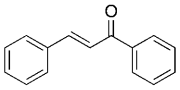
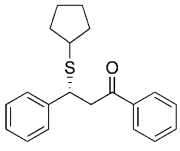
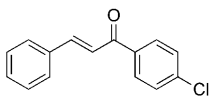
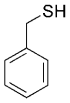
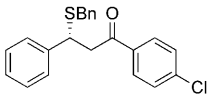
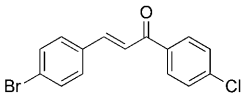
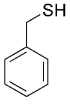
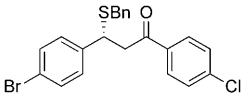
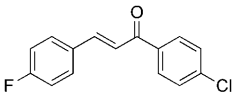
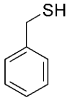
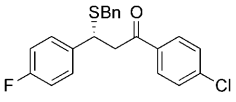
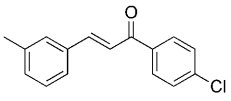
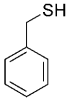
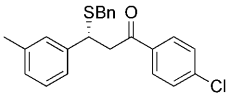
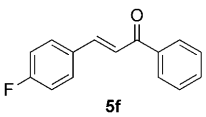
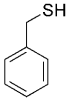
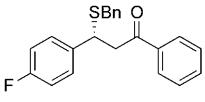
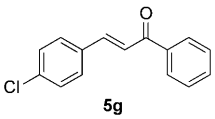
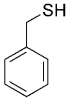
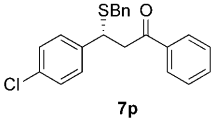
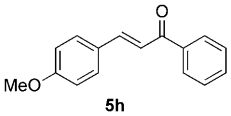
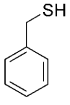
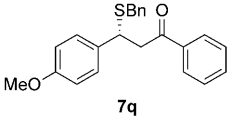
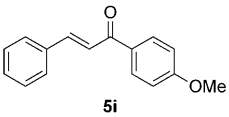
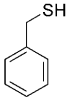
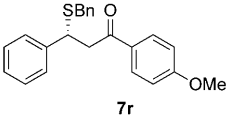
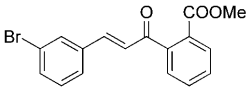
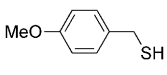
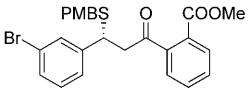
Entry	*trans*-Chalcone	Thiol	Product	*t* [h][b]	Yield [%][c]	*ee* [%][d]
1	 **5a**	 **6b**	 **7b**	1	92	70
2	 **5a**	 **6c**	 **7c**	12	86	95
3	 **5a**	 **6d**	 **7d**	12	81	93
4	 **5a**	 **6e**	 **7e**	24	80	96
5	 **5a**	 **6f**	 **7f**	24	80	96
6	 **5a**	 **6g**	 **7g**	38	88	74
7	 **5a**	 **6h**	 **7h**	72	61	80
8	 **5a**	 **6i**	 **7i**	168 40[e]	55 52	85 84
9	 **5a**	 **6j**	 **7j**	70	65	61

Table 2. (Continued)

Entry	*trans*-Chalcone	Thiol	Product	*t* [h][b]	Yield [%][c]	*ee* [%][d]
10	 **5b**	 **6a**	 **7k**	12	89	92
11	 **5c**	 **6a**	 **7l**	24	92	98
12	 **5d**	 **6a**	 **7m**	24	90	99
13	 **5e**	 **6a**	 **7n**	12	86	96
14	 **5f**	 **6a**	 **7o**	12	87	96
15	 **5g**	 **6a**	 **7p**	12	88	96
16	 **5h**	 **6a**	 **7q**	24	82	88
17	 **5i**	 **6a**	 **7r**	24	81	90
18	 **5j**	 **6k**	 **7s**	30	80	83

[a] The reaction between chalcones (0.25 mmol) and thiols (0.375 mmol) was carried out in 1 mL toluene in the presence of 1 mol% **4e** at room temperature.
[b] Reaction time.
[c] Yield of isolated product.
[d] Determined by HPLC analysis using a Chiracel OJ-H or OD-H column.
[e] Catalyst loading: 10 mol%.

for sterically hindered or allyl thiols (entries 5–9). For the addition of the less reactive *tert*-butyl thiol, the reaction could be accelerated by increasing the catalyst loading to 10 mol% so that the equilibrium could be reached within 40 h. However, the conversion stayed the same (entry 8). The reaction was then extended to a variety of *trans*-chalcones with benzyl thiol. The Michael acceptors with halogen- or alkyl-substituents furnished good yields and *ee* values regardless of their electronic properties (entries 10–15). Slightly diminished enantioselectivities were observed for chalcones

bearing hydrogen bond accepting substituents, such as carbonyl or ether groups (entries 16–18).

In conclusion, we have prepared a variety of bifunctional squaramide organocatalysts and identified **4e** as a most efficient and enantioselective catalyst for the conjugate addition of various thiols to *trans*-chalcones. This process is characterized by mild conditions, high stereocontrol and excellent yields. An inverstigation on the full scope of this new catalyst in asymmetric transformations is ongoing in our laboratory.

Experimental Section

Typical Procedure for the Organocatalytic Sulfa-Michael Addition to *trans*-Chalcone

To a solution of *trans*-chalcone **5a** (0.25 mmol) in toluene (1 mL) was added squaramide catalyst **4e** (1.5 mg, 0.0025 mmol) and benzyl thiol **6a** (1.5 equiv.). After stirring at room temperature for 3 h, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography to give **7a** as a white solid.

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