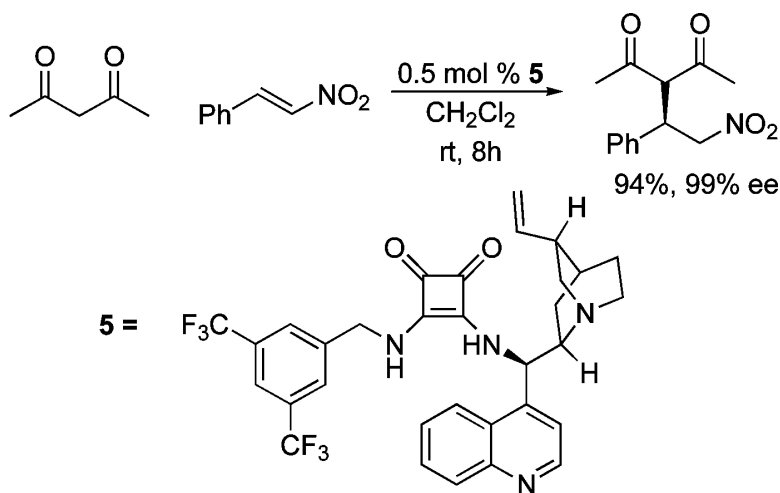


Chiral Squaramide Derivatives are Excellent Hydrogen Bond Donor Catalysts

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Chiral Squaramide Derivatives are Excellent Hydrogen Bond Donor Catalysts

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Hydrogen bonding promoted asymmetric catalysis has grown explosively over the past decade.¹ Of the different H-bond donor catalysts reported to date, those based on the thiourea core dominate the field.² The many reactions that have been promoted by thioureas underscores the importance of this “privileged” platform.³ Inasmuch as chiral thioureas have proven to be a gold mine for catalyst discovery, other H-bond donor motifs have been much less explored.⁴ We describe here the development and successful demonstration of a new family of H-bonding catalysts based on the squaramide catalophore.

Essential to the overwhelming success of thiourea-based catalysts is its ability to form two H-bonds to a reactant. The second H-bond not only further activates the reactant but also constrains it to a well-defined orientation, required for asymmetric induction. Examination of crystallographic and computational data on the thiourea unit shows that the two H atoms are positioned ~ 2.1 Å apart, each canted in by $\sim 6^\circ$ (Figure 1).⁵ The distance between the two hydrogens is defined by the fact that the accompanying N atoms are connected by a one-carbon link. We postulated that bisamides of squaric acid, which position the two hydrogens 0.6 Å further apart, could serve as a versatile core activation unit for dual H-bonding catalysts.^{6,7}

To assess the utility of squaramides for asymmetric catalysis, several differentially substituted chiral derivatives were synthesized. These compounds are easy to prepare, as shown for the preparation of **5** (Scheme 1). Stirring dimethyl squarate with an amine in CH_2Cl_2 promotes the first substitution reaction. Repeating the process with a second amine gives the disubstituted squaramide, which precipitates out of solution. The crystal structure of squaramide **5** displayed a distance of 2.85 Å between the acidic H atoms (Figure 2), approximating the calculated distance.

A brief survey of different chiral squaramides identified the (–)-cinchonine-substituted derivative (**5**) to be an effective H-bond donor catalyst for the conjugate addition of 2,4-pentanedione (**6**) to β -nitrostyrene (**7**), one of the earliest reactions to be catalyzed using a simple chiral thiourea.⁸ When this reaction was carried out in ether at room temperature with 2.0 mol % of **5**, the conjugate addition product **8** was obtained in 88% yield and 96% ee, a result that compares favorably with previous reports on this transformation (Table 1, entry 1).^{9,10} The same reaction in toluene gave the product in higher yield and ee (entry 2). The best result was obtained with methylene chloride: the reaction proceeded faster and in higher yield and ee (entry 3). The improved enantioselectivity was maintained when the catalyst loading was reduced to 0.5 mol % (entry 4). Indeed, the reaction proceeds well even at 0.1 mol % catalyst loading, with only slight erosion in the observed ee (entry 5).

The scope of this squaramide catalyzed conjugate addition reaction was examined next. Various substituted β -nitrostyrenes were reacted with 2,4-pentanedione (**6**) in the presence of 0.5 mol % of **5**, and all afforded consistently high yields and enantioselectivities (Table 2). A somewhat longer reaction time was required for 4-methoxy- β -nitrostyrene due to its inherently lower reactivity toward nucleophiles, but it still gave excellent results (entry 2). Halogen substitution was uniformly well tolerated (entries 3–5).

Given the consistently good results obtained with different styrenes, we next examined the possibility of using various 1,3-dicarbonyl com-

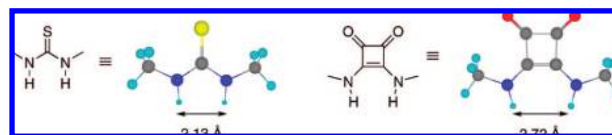
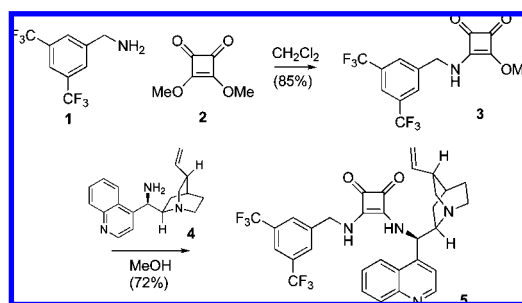


Figure 1. Calculated H-bond distances in *N,N'*-dimethylthiourea and *N,N'*-dimethylsquaramide.

Scheme 1. Synthesis of Chiral Squaramide Catalyst **5**



pounds as nucleophiles (**11**; Table 3). Of the dozen nucleophiles utilized, all gave the conjugate addition products in good to excellent yields. Although several of the reactions proceeded with little diastereoselectivity, each of the diastereomers was formed in very good to excellent enantioselectivity. Cyclopentanones **11j** and **11k** proved to be exceptions, giving the products with high diastereoselectivity. In all these reactions, squaramide **5** is believed to operate as a bifunctional catalyst, analogously to Takemoto's catalyst.⁸

The results presented above show the squaramide unit to be an effective scaffold on which to build chiral H-bond donor catalysts. For the conjugate

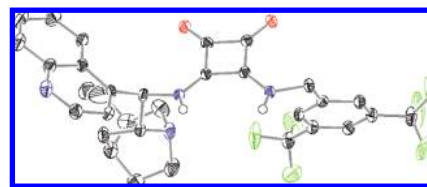
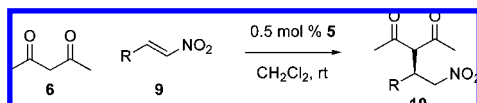


Figure 2. ORTEP of squaramide **5**.

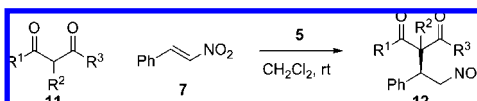
Table 1. Evaluation of **5** as a Catalyst for the Conjugate Addition of 2,4-Pentanedione to β -Nitrostyrene

entry	mol % of 5	solvent	time	yield	ee
1	2.0	Et ₂ O	24 h	88%	96%
2	2.0	PhMe	24 h	94%	98%
3	2.0	CH ₂ Cl ₂	7 h	98%	>99%
4	0.5	CH ₂ Cl ₂	8 h	94%	>99%
5	0.1	CH ₂ Cl ₂	20 h	97%	96%

Table 2. Variation of Electrophile in Reaction with **6**^a

entry	nitroolefin	product	time	yield	ee
1	9a	10a	9 h	98%	97%
2	9b	10b	24 h	99%	98%
3	9c	10c	10 h	89%	98%
4	9d	10d	12 h	98%	97%
5	9e	10e	10 h	98%	98%
6	9f	10f	8 h	96%	97%
7	9g	10g	9 h	98%	98%
8	9h	10h	20 h	96%	97%
9	9i	10i	10 h	98%	97%

^a Reactions were carried out on 0.500 mmol of **9** with 2.0 equiv of **6** and 0.5 mol % **5** in 1.5 mL of CH₂Cl₂.

Table 3. Variation of Nucleophile in Reaction with **7**

entry	nucleophile	product	time	yield (dr)	ee ^a
1 ^b	11a	12a	9 h	91% (2:1)	95%, 94%
2 ^b	11b	12b	24 h	93%	88%
3 ^b	11c	12c	8 h	97% (1.4:1)	92%, 81%
4 ^c	11d	12d	18 h	75% (1:1)	96%, 98%
5 ^c	11e	12e	8 h	89% (1.6:1)	97%, 96%
6 ^c	11f	12f	12 h	95% (1.6:1)	96%, 96%
7 ^c	11g	12g	9 h	90% (5:1)	96%, 90%
8 ^c	11h	12h	8 h	83% (1.3:1)	94%, 86%
9 ^c	11i	12i	24 h	90% (2:1)	92%, 83%
10 ^c	11j	12j	24 h	96% (18:1)	98%, 96%
11 ^c	11k	12k	24 h	75% (50:1)	93%, 77%
12 ^c	11l	12l	12 h	65% (4:1)	94%, 91%

^a Values are listed for major and minor diastereomers respectively.

^b Reaction was carried out with 0.500 mmol of **7**, 2.0 equiv of **11**, and 0.5 mol % **5** in 1.5 mL of CH₂Cl₂. ^c Reaction was carried out with 0.200 mmol of **7**, 2.0 equiv of **11**, and 2.0 mol % **5** in 0.6 mL of CH₂Cl₂.

addition reactions of 1,3-dicarbonyl compounds to nitroolefins, cinchona derivative **5** was a remarkably active catalyst, affording the conjugate addition products in high yields and enantioselectivities. The modular nature of the synthesis means that a wide range of squaramide catalysts, tuned with regard to the p*K*_a of the hydrogens as well as the chiral environment, should be readily accessible. Further investigation of these catalysts, as well as structures in which the distance between the donor hydrogens is increased even further, can be expected to open new opportunities for H-bond mediated asymmetric catalysis.

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Supporting Information Available: Procedure for catalyst preparation, characterization data, NMR spectra for new compounds, and HPLC data for conjugate addition products. This information is available free of charge via the Internet at <http://www.pubs.acs.org>.

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