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Chiral Squaramide Derivatives are Excellent Hydrogen Bond Donor Catalysts

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Abstract

Thioureas represent the dominant platform for hydrogen bond promoted asymmetric catalysts. A large number of reactions, reported in scores of publications, have been successfully promoted by chiral thioureas. The present paper reports the use of squaramides as a highly effective new scaffold for the development of chiral hydrogen bond donor catalysts. squaramide catalysts are very simple to prepare. The (-)-cinchonine modified squaramide (**5**), easily prepared through a two step process from methyl squarate, was shown to be an effective catalyst, even at catalyst loadings as low as 0.1 mol%, for the conjugate addition reactions of 1,3-dicarbonyl compounds to β -nitrostyrenes. The addition products were obtained in high yields and excellent enantioselectivities.

Hydrogen bonding promoted asymmetric catalysis has grown explosively over the past decade.¹ Of the different hydrogen bond donor catalysts reported to date, those based on the thiourea core dominate the field.² The many reactions, reported in scores of publications, 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 hydrogen bond donor motifs have been much less explored.⁴ We describe here the development and successful demonstration of a new family of hydrogen bonding catalysts based on the squaramide catalophore.

Essential to the overwhelming success of thiourea-based catalysts is its ability to form two hydrogen bonds to a reactant. The second hydrogen 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 hydrogen atoms are positioned approximately 2.1 Å apart, each canted in by ~6°. The distance between the two hydrogens is defined by the fact that the accompanying nitrogen 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 hydrogen 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 CH₂Cl₂ 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 hydrogen atoms (Figure 2), approximating the calculated distance.

A brief survey of different chiral squaramides identified the (-)-cinchonine-substituted derivative (**5**) to be an effective hydrogen 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 higher ee (entry 2). The best result was obtained methylene chloride: the reaction proceeded faster, in higher yield and higher 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). 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 compounds 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 diastereomer 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 hydrogen bond donor catalysts. For the conjugate 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 pK_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 hydrogen bond mediated asymmetric catalysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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10. The absolute stereochemistry of **8** was assigned by comparison of the optical rotation with the value determined in Ref 9e.

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

Figure 2.
ORTEP of squaramide **5**

Scheme 1.
Synthesis of chiral squaramide catalyst **5**

Table 1
Evaluation of **5** as a catalyst for the conjugate addition of 2,4-pentanedione to β -nitrostyrene

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

Table 2

Variation of electrophile in reaction with **6^a**

entry	nitroolefin		product	time	yield	ee
	9a	9b				
1			10a	9 h	98%	97%
2			10b	24 h	99%	98%
3			10c	10 h	89%	98%

entry	nitroolefin	product	time	yield	ee
4	<p>9d</p>	10d	12 h	98%	97%

entry	nitroolefin	product	time	yield	ee
5		10e	10 h	98%	98%
6		10f	8 h	96%	97%

entry	nitroolefin	product	time	yield	ee
7			9 h	98%	98%

Table 3

entry	nucleophile	product	time	yield (dr)	ee ^b
11a		12a	9 h	91% (2:1)	95%, 94%

entry	nucleophile	product	time	yield (dr)	ee ^b
2 ^b		12b	24 h	93%	88%

entry

nucleophile

product

time

yield (dr)

ee^b

11c

3^b

92%, 81%

97% (1.4:1)

8 h

12c

entry	nucleophile	product	time	yield (dr)	ee ^b
4 ^c		12d	18 h	75% (1:1)	96%, 98%

11d

entry	nucleophile	product	time	yield (dr)	ee ^b
5 ^c		12e	8 h	89% (1.6:1)	97%, 96%

entry	nucleophile	product	time	yield (dr)	ee ^b
6 ^c		12f	12 h	95% (1.6:1)	96%, 96%

entry	nucleophile	product	time	yield (dr)	ee ^b
7 ^c		12g	9 h	90% (5:1)	96%, 90%
8 ^c		12h	8 h	83% (1.3:1)	94%, 86%
9 ^c		12i	24 h	90% (2:1)	92%, 83%

entry

nucleophile

product

time

yield (dr)

ee^b

10^c

11j

12j

24 h

96% (18:1)

98%, 96%

entry	nucleophile	product	time	yield (dr)	ee ^b
11 ^c		12k	24 h	75% (50:1)	93%, 77%

entry

nucleophile

product

time

yield (dr)

ee^b

12^c

111

121

12 h

65% (4:1)

94%, 91%

entry

nucleophile

product

time

yield (dr)

ee^b