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Highly Enantioselective Michael Addition of Nitroalkanes to Chalcones Using Chiral Squaramides as Hydrogen Bonding Organocatalysts

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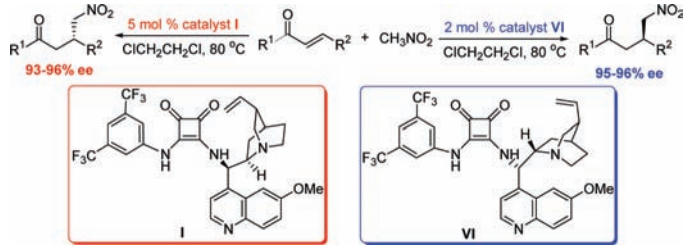
ABSTRACT



A series of squaramide-based organocatalysts were facilely synthesized and applied as hydrogen bonding organocatalysts in the enantioselective Michael addition of nitroalkanes to chalcones. These organocatalysts promoted the Michael addition with low catalyst loading under high temperature (80 °C), affording the desired *R* or *S* enantiomers of the products flexibly in high yields with excellent enantioselectivities (93−96% ee) by the appropriate choice of organocatalysts.

The utilization of hydrogen bonding as an activation force is widespread in asymmetric organocatalysis. In the past decade, chiral ureas and thioureas, diols, and phosphoric acids dominated the field of hydrogen bonding, and great advances were achieved.[1] Given the importance of hydrogen bonding catalysts in asymmetric organocatalysis, the design and development of new hydrogen bonding catalysts is of great interest. In 2008, Rawal first reported novel chiral squaramide derivatives as hydrogen bonding organocatalysts for the conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes, in which excellent results were achieved.[2] In the past two years, a series of squaramide-based catalysts were developed and successfully applied in various asymmetric reactions such as enantioselective Michael addition, Friedel−Crafts reaction, and α-amination of 1,3-dicarbonyl compounds.[3] These pioneering works demonstrate that squaramide derivatives can serve as good hydrogen bonding organocatalysts in asymmetric catalysis. Meanwhile, another report about the application of squaramide-based organocatalysts in organic reaction has also appeared.[4] Thus, the development of new squaramides and extending their applications in various reactions are challenging tasks.

The enantioselective conjugate addition of carbanion nucleophiles to electron-deficient α,β-unsaturated compounds

(1) For selected reviews, see: (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (b) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418. (e) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (f) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (g) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.

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is one of the most important C−C bond forming reactions in organic synthesis.[5] Among various carbanion nucleophiles, nitroalkanes have been demonstrated to be a valuable stabilized carbanion for the conjugate addition due to the strong electron-withdrawing nature of the nitro group and its potent transformation to a variety of valuable functional groups.[6] In the case of nitroalkanes, the products of the Michael addition to chalcones are useful intermediates for a variety of further elaborated structures such as chiral aminocarbonyls, pyrrolidines, γ-lactams, and γ-amino acids.[7] To the best of our knowledge, after the pioneering report on asymmetric Michael addition of nitromethane to chalcone was reported,[8a] considerable efforts have been devoted to the asymmetric Michael addition of nitroalkanes to α,β-unsaturated ketones in the past decades;[8,9] however, only a few examples with excellent results have been reported for the asymmetric Michael addition of nitroalkanes to chalcones. Therefore, searching for suitable catalytic systems with high catalytic activity and enantioselectivity is still challenging and demanding. Herein, we would like to document the development of a series of chiral squaramide-based organocatalysts for the enantioselective Michael addition of nitroalkanes to chalcones. The desired products were obtained in high yields (up to 99%) with excellent enantioselectivities (93−96% ee).

To assess the ability of chiral squaramides for the enantioselective Michael addition of nitroalkanes to chalcones, a series of catalysts with various substituents **I**−**IX** (Figure 1) were synthesized. It is noteworthy that these quaramide-based organocatalysts can be readily prepared in three steps from commercially available dimethyl squarate, aromatic amines, and cinchona alkaloids, and possess high modular nature. The facile synthesis and high modular nature facilitate the fine-tuning of their catalytic activity in organic reactions.

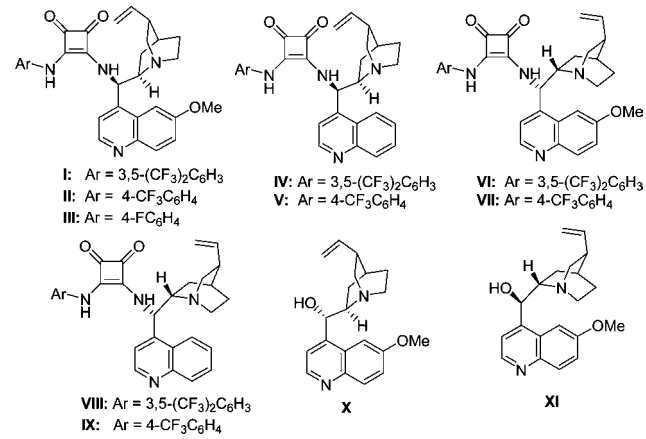
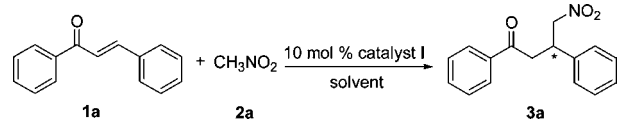


Figure 1. Structures of screened organocatalysts.

Considering the bifunctional nature of the catalysts, we expected them to promote the enantioselective Michael addition of nitroalkanes to chalcones. Our initial screening reaction between nitromethane and chalcone was performed in the presence of 10 mol % catalyst **I** in CH_2Cl_2, and the desired product was obtained in 56% yield and 88% ee at room temperature for 72 h. For optimization of the reaction conditions, we screened the effect of solvents and temperature. The results are summarized in Table 1. Variation of the solvents had a pronounced effect on the course of the reaction. The proton solvent MeOH gave poorer yield and very lower enantioselectivity (entry 2), while using THF led to an increase in the enantioselectivity (92% ee), but an

Table 1. Screening of Reaction Conditions for the Conjugate Addition of Nitromethane to Chalcone[a]



1a 2a 3a

entry	solvent	t (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	25	72	56	88 (*S*)[d]
2	MeOH	25	72	38	18 (*S*)
3	THF	25	72	8	92 (*S*)
4	$ClCH_2CH_2Cl$	25	72	62	90 (*S*)
5	CH_3NO_2	25	72	93	85 (*S*)
6	$ClCH_2CH_2Cl$	50	72	90	92 (*S*)
7	$ClCH_2CH_2Cl$	80	48	97	94 (*S*)
8	toluene	110	48	94	93 (*S*)
9	C_6H_5Cl	130	48	92	93 (*S*)

[a] Unless noted otherwise, reactions were carried out with 0.25 mmol of chalcone and 2.5 mmol of nitromethane in 0.5 mL of solvent. [b] Isolated yields. [c] Determined by HPLC. [d] Absolute configuration was determined by comparison of the optical rotation with literature data.[8]

(5) For selected recent reviews on enantioselective conjugate additions, see: (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (c) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123. (d) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

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(8) For selected examples of asymmetric Michael addition of nitroalkanes to chalcones, see: (a) Colonna, S.; Hiemstra, H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1978**, 238. (b) Wang, L.; Zhang, Q.; Zhou, X.; Liu, X.; Lin, L.; Qin, B.; Feng, X. *Chem.—Eur. J.* **2010**, *16*, 7696. (c) Hua, M.; Cui, H.; Wang, L.; Nie, J.; Ma, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2772. (d) Vakulya, B.; Varga, S.; Soós, T. *J. Org. Chem.* **2008**, *73*, 3475. (e) Suresh, P.; Pitchumani, K. *Tetrahedron: Asymmetry* **2008**, *19*, 2037. (f) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (g) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331. (h) Sundararajan, G.; Prabagaran, N. *Org. Lett.* **2001**, *3*, 389. (i) Funabashi, K.; Saida, Y.; Kanai, M.; Arai, T.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7557.

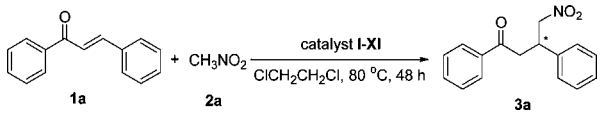
(9) For selected recent examples of asymmetric Michael addition of nitroalkanes to other unsaturated enones, see: (a) Mei, K.; Jin, M.; Zhang, S.; Li, P.; Liu, W.; Chen, X.; Xue, F.; Duan, W.; Wang, W. *Org. Lett.* **2009**, *11*, 2864. (b) Li, P.; Wang, Y.; Liang, X.; Ye, J. *Chem. Commun.* **2008**, 3302. (c) Palomo, C.; Pazos, R.; Oiarbide, M.; García, J. M. *Adv. Synth. Catal.* **2006**, *348*, 1161. (d) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313. (e) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897. (f) Mitchell, C. E. T.; Brenner, S. E.; Ley, S. V. *Chem. Commun.* **2005**, 5346. (g) Ooi, T.; Takada, S.; Fujioka, S.; Maruoka, K. *Org. Lett.* **2005**, *7*, 5143. (h) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975.

unacceptable yield (entry 3). Compared with CH_2Cl_2, 1,2-dichloroethane gave better results (62% yield, 90% ee) (entry 4). When the reaction was carried out in neat nitromethane, much higher yield and a little lower enantioselectivity (85% ee) were achieved (entry 5). To improve the rate of the reaction, the reaction temperature was evaluated by using 1,2-dichloroethane as the best solvent. Interestingly, the product was obtained in high yield with a slightly increased enantioselectivity (92% ee) at 50 °C (entry 6). When the reaction temperature was further elevated to 80 °C, a nearly complete conversion and higher enantioselectivity (94% ee) were achieved within 48 h (entry 7). The reason for the higher enantioselectivity observed at higher temperature is not clear. We then turned our attention to higher boiling solvents (toluene and chlorobenzene), but no better result was obtained (entries 8 and 9).

After finding the optimized solvent and reaction temperature, the screening of the squaramide-based organocatalysts **I**−**IX** was conducted under the optimized conditions. As summarized in Table 2, the fine-tuning of catalyst structure had a very limited effect on the enantioselectivities. Comparable high enantioseletivities (92−94% ee) were obtained in all the cases. Noticeably, the quinidine- and cinchonine-derived catalysts **I**−**V** gave the *S*-configured products, whereas the quinine- and cinchonidine-derived catalysts **VI**−**IX** provided the *R*-configured products with the same efficiency. It is also noted that the acidity of the hydrogen bond donor motifs had a certain effect on their catalytic activity. The catalysts with 3,5-$(CF_3)_2$ substitution on the aromatic ring gave better yields than the ones with 4-CF_3 and 4-F substitutions, which demonstrated that the activity of the catalyst was improved with the increasing of the acidity. Quinidine **X** and quinine **XI** were also tested for comparison, but very low yields and enantioselectivities were observed. Obviously, the best catalysts were **VI** and **I**, which gave the *R* and *S* enantiomers in excellent yields and enantioselectivities, respectively (>99% yield and 94% ee, 97% yield and 94% ee). With the best catalysts in hand, the effect of catalyst loading was further investigated. When the catalyst **VI** loading was reduced to 5 mol %, a comparable result (99% yield and 95% ee) was still achieved. Catalyst loading of 2 and 1 mol % could also maintain the enantioselectivities, albeit with decreased yields. Compromising with the yield, 2 mol % catalyst loading was chosen for catalyst **VI**. Catalyst **I** gave lower reactivity than catalyst **VI**, and 5 mol % catalyst loading was our choice.

Under the optimized conditions with 2 mol % catalyst **VI**, a diverse array of substituted chalcones were examined. The results are summarized in Table 3. The electronic property of the substituents on the phenyl ring did not have an evident effect on the enantioselectivity, but a little effect on the yield. All the substrates reacted smoothly with nitromethane to give the expected *R* enantiomers of the products in excellent enantioselectivities (95−96% ee). Chalcones bearing both electron-withdrawing and weak electron-donating substitutions provided the desired products in excellent yields, while strong electron-donating substitution MeO led to decreased yields. The position of substituents also influenced the enantioselectivities and yields slightly.

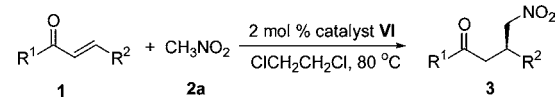
Table 2. Screening of Organocatalysts and Catalyst Loading for the Michael Addition of Nitromethane to Chalcone[a]



entry	catalyst	loading (mol %)	yield (%)[b]	ee (%)[c]
1	**I**	10	97	94 (*S*)[d]
2	**II**	10	92	93 (*S*)
3	**III**	10	73	93 (*S*)
4	**IV**	10	93	93 (*S*)
5	**V**	10	81	92 (*S*)
6	**VI**	10	>99	94 (*R*)[d]
7	**VII**	10	84	94 (*R*)
8	**VIII**	10	94	94 (*R*)
9	**IX**	10	80	94 (*R*)
10	**X**	10	13	33 (*R*)
11	**XI**	10	12	19 (*S*)
12	**VI**	5	99	95 (*R*)
13	**VI**	2	89	95 (*R*)
14	**VI**	1	69	95 (*R*)
15	**I**	5	89	95 (*S*)
16	**I**	2	62	95 (*S*)

[a] Unless noted otherwise, reactions were carried out with 0.25 mmol of chalcone and 2.5 mmol of nitromethane in 0.5 mL of CH_2ClCH_2Cl. [b] Isolated yields. [c] Determined by HPLC, using a Chiralpak IA column. [d] Absolute configuration was determined by comparison of the optical rotation with literature data.[8]

Table 3. Enantioselective Michael Addition of Nitroalkanes to Various Chalcones Using Catalyst **VI**[a]

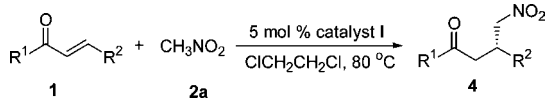


entry	R^1	R^2	product	yield (%)[b]	ee (%)[c]
1	C_6H_5	C_6H_5	**3a**	94	95(*R*)[d]
2	C_6H_5	4-MeC_6H_4	**3b**	91	95 (*R*)
3	C_6H_5	4-$MeOC_6H_4$	**3c**	81	95 (*R*)
4	C_6H_5	4-ClC_6H_4	**3d**	99	95 (*R*)
5	C_6H_5	4-BrC_6H_4	**3e**	96	95 (*R*)
6	C_6H_5	2-BrC_6H_4	**3f**	93	96 (*R*)
7	4-MeC_6H_4	C_6H_5	**3g**	91	96 (*R*)
8	4-$MeOC_6H_4$	C_6H_5	**3h**	78	96 (*R*)
9	3-$MeOC_6H_4$	C_6H_5	**3i**	66	95 (*R*)
10	4-FC_6H_4	C_6H_5	**3j**	98	96 (*R*)
11	4-ClC_6H_4	C_6H_5	**3k**	98	95 (*R*)
12	4-BrC_6H_4	C_6H_5	**3*l***	98	96 (*R*)
13	4-MeC_6H_4	4-MeC_6H_4	**3m**	86	96 (*R*)
14	4-ClC_6H_4	4-ClC_6H_4	**3n**	99	95 (*R*)

[a] Unless noted otherwise, reactions were carried out with 0.25 mmol of chalcones and 2.5 mmol of nitromethane or nitroethane in 0.5 mL of CH_2ClCH_2Cl at 80 °C for 60 h. [b] Isolated yields. [c] Determined by HPLC, using a Chiralpak IA column. [d] Absolute configuration was determined by comparison of the optical rotation with literature data.[8]

It is well-known that the *R* and *S* enantiomers commonly show very different biological activities. The facile access to both the *R* and *S* enantiomers of the products is of great importance in the asymmetric catalysis. To our delight, during the catalyst structure screening, both the *R* and *S* enantiomers of the products can be obtained in excellent yields and enantioselectivities respectively with catalysts **IV** and **I**. The same substrate scope was explored in the presence of 5 mol % catalyst **I** and the *S* enantiomers of the products were obtained in good to high yields with excellent enantioselectivities (93−96% ee). As shown in Table 4, a similar tendency of the substituent effect on enantioselectivies was observed.

Table 4. Asymmetric 1,4-Addition of Nitroalkanes to Various Chalcones Using Catalyst **I**[a]

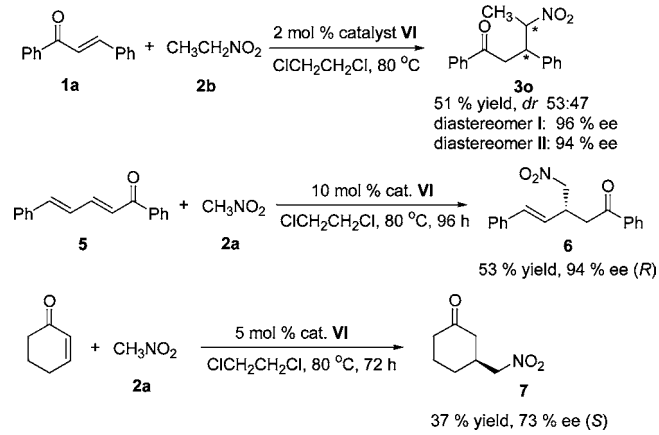


entry	R^1	R^2	product	yield (%)[b]	ee (%)[c]
1	C_6H_5	C_6H_5	**4a**	94	95 (*S*)[d]
2	C_6H_5	4-MeC_6H_4	**4b**	92	94 (*S*)
3	C_6H_5	4-MeOC_6H_4	**4c**	70	95 (*S*)
4	C_6H_5	4-ClC_6H_4	**4d**	99	94 (*S*)
5	C_6H_5	4-BrC_6H_4	**4e**	98	95 (*S*)
6	C_6H_5	2-BrC_6H_4	**4f**	98	93 (*S*)
7	4-MeC_6H_4	C_6H_5	**4g**	94	96 (*S*)
8	4-MeOC_6H_4	C_6H_5	**4h**	84	95 (*S*)
9	3-MeOC_6H_4	C_6H_5	**4i**	64	94 (*S*)
10	4-FC_6H_4	C_6H_5	**4j**	96	96 (*S*)
11	4-ClC_6H_4	C_6H_5	**4k**	98	95 (*S*)
12	4-BrC_6H_4	C_6H_5	***4l***	95	95 (*S*)
13	4-MeC_6H_4	4-MeC_6H_4	**4m**	87	95 (*S*)
14	4-ClC_6H_4	4-ClC_6H_4	**4n**	99	94 (*S*)

[a] Unless noted otherwise, reactions were carried out with 0.25 mmol of chalcones and 2.5 mmol of nitromethane in 0.5 mL of CH_2ClCH_2Cl at 80 °C for 60 h. [b] Isolated yields. [c] Determined by HPLC, using a Chiralpak IA column. [d] Absolute configuration was determined by comparison of the optical rotation with literature data.[8]

In addition, the reaction of nitroethane **2b** and chalcone **1a** catalyzed by 2 mol % catalyst **VI** was also effective to provide the corresponding products with high enantioselectivities for both diastereomers (96% ee and 94% ee, respectively), albeit with moderate yield and low diastereoselectivities (Scheme 1). The asymmetric Michael addition of nitromethane **2a** to (2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one **5** with use of 10 mol % catalyst **VI** was investigated. As shown in Scheme 1, the substrate **5** gave the desired product **6** in moderate yield and excellent enantioselectivity in a longer time due to its lower reactivity. The asymmetric Michael addition of nitromethane to other linear or cyclic enones was also investigated. No reaction occurred for 1-phenyl-2-buten-1-one, and 2-cyclohexen-1-one only gave product **7** in 37% yield with 73% ee.

Scheme 1. Further Investigation of Substrates Scope



On the basis of the configuration of the product (+)-**3a**, a possible transition state model is hypothesized and shown in the Supporting Information. We envisioned that the chiral squaramide-based catalyst **VI** acts in a bifunctional fashion. The chalcone is fixed and activated by the squaramide moiety through double hydrogen bonding between the NH groups and the carbonyl group. Meanwhile, the nitromethane is activated by the basic quinine nitrogen atom. Then the *R* product (+)-**3a** could be generated by the *Re*-face attack of the activated chalcone.

In conclusion, we have developed a new series of chiral suqaramide cinchona alkaloid-based organocatalysts which were effective in promoting the asymmetric Michael addition of nitroalkanes to chalcones with low catalyst loading. These catalysts could be readily prepared and possess a high modular nature. Remarkably, catalysts **VI** and **I** were employed to catalyze the Michael addition of nitromethane to chalcones at 80 °C, and both the *R* and *S* enantiomers of the products were easily obtained in high yields with excellent enantioselectivities (93−96% ee), respectively. This class of chiral squaramide-based catalysts is a kind of good hydrogen-bonding organocatalyst, and current studies are underway to broaden their applications in asymmetric catalysis.

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Supporting Information Available: Experimental procedures and characterizations, copies of ^1H NMR and ^{13}C NMR of new compounds, and HPLC profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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