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C_3-Symmetrical Cinchonine-Squaramide as New Highly Efficient, and Recyclable Organocatalyst for Enantioselective Michael Addition

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Abstract: A novel and recyclable catalyst, a C_3-symmetrical cinchonine-squaramide, has been developed for the asymmetric Michael addition of 1,3-dicarbonyl compounds to nitroalkenes. When using only 1 mol% of catalyst **1a** for the reaction, high reaction yields with excellent enantioselectivities and diastereoselectivities (up to 96% yield, >99% *ee*, >99:1 *dr*) were achieved, in which the results for cyclic keto esters are the best ever achieved. Moreover, **1a** can be easily recovered by simple precipitation and was used for six cycles without losing any selectivity and activity.

Keywords: asymmetric Michael addition; C_3-symmetrical species; catalyst recycling; cinchonine-squaramide

Introduction

The asymmetric Michael addition has emerged as one of the most efficient and powerful tools to C–C bond formation in organic synthesis.[1] In particular, the asymmetric Michael addition of 1,3-dicarbonyl compounds to nitroalkenes catalyzed by organocatalysts such as diamine,[2] amine-thiourea,[3] *Cinchona* derivatives[4] etc. is one of the most important methods for the preparation of optically active nitro carbonyl compounds,[5] which are the key intermediates for preparation of a large number of pharmaceutical substances. In 2008, the chiral squaramide organocatalysts pioneered by Rawal's group have been demonstrated to be a new family of efficient and versatile bifunctional organocatalysts for asymmetric additions of 1,3-dicarbonyl compounds to nitrostyrenes with excellent enantioselectivity.[6] Despite important progress in this area, there is still room for improvement regarding this type of asymmetric Michael addition reaction. For example, slight erosions in enantioselectivities and diastereoselectivities in addition to heterocyclic nitroolefins are still a challenge. Furthermore, due to the difficulty in catalyst recycling, the applications of these catalytic systems in pharmaceutical production have been limited. Therefore, new strategies to design efficient, recyclable chiral catalysts for the asymmetric Michael addition reaction are highly desirable.

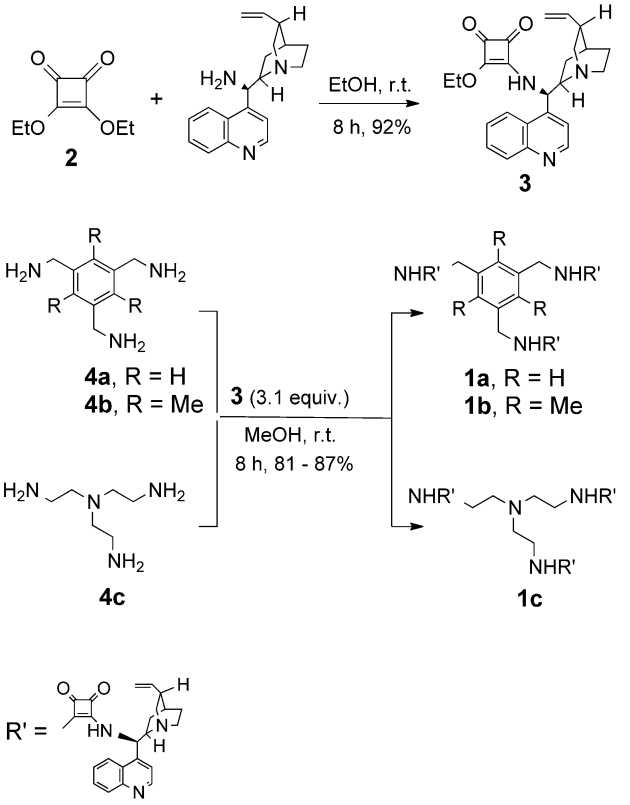
Currently, C_3-symmetrical chiral molecules have drawn much attention in the area of supramolecular coordination chemistry,[7] molecular recognition,[8] and material sciences.[9] As far as asymmetric catalysis is concerned, it is generally believed that C_3-symmetrical ligands can reduce the number of possible diastereomers in catalytic intermediates, and create a more sterically encumbered chiral space as well, which might reduce disadvantages such as rotation and flexibility in enantiofacial control. In addition, C_3-symmetrical ligands can also be synthesized in a direct or modular way, which can greatly improve the ligand diversity and provides access to ligands capable of achieving excellent selectivity for a wide range of asymmetric reactions. Since 1998, the chiral C_3-symmetrical ligands have been assayed in reactions such as asymmetric cyclopropanation, allylic oxidation, alkynylation of aldehydes, allylic alkylation, and asymmetric borane reduction of proketones giving modest to good enantioselectivities.[10] More recently, Reetz and co-workers reported the use of the C_3-symmetrical monodentate phosphate ligand in the Rh-catalyzed enantioselective hydrogenation of homoallylic alcohols.[11] Meanwhile, squaric acid has long been

known as an aromatic compound with a unique character and wide applications,[12] its rigid ring provides an efficient environment for coordination of the substrates and the reagents in asymmetric reactions.[13,14] In consideration of the excellent performance of the squaramide organocatalysts developed by Rawal's group and later exploited by other groups,[6,13] we anticipated that the synthesis of C_3-symmetrical catalysts with a squaric acid moiety, would not only provide a unique chiral environment in asymmetric transformation, but also open a new way for the design and synthesis of novel organocatalysts. To the best of our knowledge, there is no report on the C_3-symmetrical chiral molecules of squaric acid for use in asymmetric catalysis so far. Our interest is to explore the synthesis and application of C_3-symmetrical squaramides in the enantioselective Michael addition. For this purpose, our initial efforts focused on the synthesis of C_3-symmetrical cinchonine-squaramides starting with commercially available squaric acid and cinchonine. We envisioned that the combination of a cinchonine framework and a squaric acid skeleton would enhance the enantioselectivity. Moreover, the poor solubility of the C_3-symmetrical squaramide in organic solvents enabled its easy recovery by a simple precipitation method, allowing its operational recycling. Herein, we describe the first C_3-symmetrical cinchonine-squaramide as a new robust, highly efficient, recyclable catalyst for the enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroalkenes.

On the basis of the above considerations and from the viewpoint of synthetic simplicity, three C_3-symmetrical cinchonine-squaramides **1a–c** were designed, in which the three chiral subunits of the catalysts were connected with each other *via* a C_3-symmetrical triamine core through a squaramide linker. As illustrated in Scheme 1, compounds **1a–c** were prepared in two steps *via* the coupling of diethyl squarate with cinchonine-derived amine, and subsequent condensation with amines **4a–c** in good yields under mild conditions. In a similar way, the corresponding bis- and monocinchonine-squaramides were also prepared for comparison.[15]

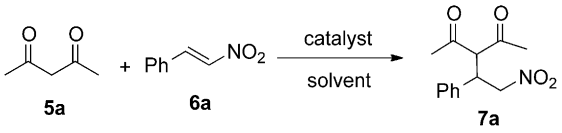
Results and Discussion

With catalysts **1a–c** in hand, an evaluation of their catalytic activities in the asymmetric Michael addition of 1,3-dicarbonyl compounds to nitroolefins was undertaken. Initially, 2,4-pentanedione (**5a**) and β-nitrostyrene (**6a**) were chosen as substrates for this study. After a brief survey of reaction conditions (Table 1), we found that the catalyst, solvent, and catalyst loading are critical determinants of the reaction efficiency. When the reaction was catalyzed by 1.0 mol% **1a** in CH_2Cl_2 with 1.1 equivalents of **5a** and 1.0 equivalent



Scheme 1. Preparation of C_3-symmetrical cinchonine-squaramides **1a--c**.

Table 1. Optimization and catalyst screening for the Michael addition of **5a** with **6a**.



Entry	Catalyst (mol%)	Solvent	Yield [%][c]	*ee* [%][d]
1[a]	**1a** (0.5)	DCM	91	86
2[a]	**1a** (1.0)	DCM	98	89
3[a]	**1a** (2.0)	DCM	95	66
4[a]	**1a** (5.0)	DCM	97	55
5[b]	**1a** (1.0)	DCM	93	97
6[b]	**1a** (1.0)	toluene	91	85
7[b]	**1a** (1.0)	THF	95	81
8[b]	**1a** (1.0)	ethanol	73	85
9[a]	**1b** (1.0)	DCM	89	63
10[a]	**1c** (0.5)	DCM	93	82
11[a]	**1c** (1.0)	DCM	97	83
12[a]	**1c** (5.0)	DCM	95	62

[a] *Reaction conditions:* 0.5 mmol of **5a**, 0.25 mmol of **6a**, indicated amount of catalysts in 1.5 mL CH_2Cl_2, room temperature, 12 h.
[b] *Reaction conditions:* 0.275 mmol (1.1 equiv.) of **5a**, 0.25 mmol of **6a**, indicated catalyst in 0.1 mL of solvent, room temperature, 12 h.
[c] Isolated yield.
[d] Determined by HPLC with an OD-H column.

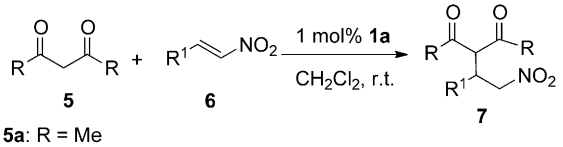
of **6a**, **7a** was obtained in high yield (93%) and excellent enantioselectivity (97% *ee)* (Table 1, entry 5). Interestingly, the catalyst loading of **1a** dramatically influenced the enantioselectivity of the product; increasing the loading of **1a** led to decreased enantioselectivity (Table 1, entries 3 and 4). While other solvents (e.g., THF, toluene, ethanol) and catalysts all provided inferior results (Table 1, entries 6–8). When **1c** was used instead of **1a** under the same reaction conditions, a decreased enantioselectivity (83% *ee*) was observed (Table 1, entry 11); on switching from **1c** to **1b**, the enantioselectivity of the reaction was even poorer (63% *ee*) (Table 1, entry 9). This implied that a steric effect was an important factor for enantioselectivity. Bearing three methyl groups on the phenyl ring, the steric hindrance of **1b** might prevent the suitable transition-state geometry to be attained easily. Under the same reaction conditions, in comparison with **1a**, both bissquaramide and monosquaramide gave moderate enantioselectivity (see Supporting Information). The results indicated that the C_3-symmmetrical squaramide **1a** was more effective in the Michael addition reaction.

With the optimized reaction conditions in hand, the scope and limitation of our catalytic system to in enantioselective Michael reactions of various nitroolefins with 1,3-dicarbonyl compounds was investigated, the results are summarized in Table 2.

As demonstrated in Table 2, with using 1 mol% **1a**, the reactions of all β-nitrostyrenes, bearing *ortho* or *para* electron-donating or electron-withdrawing substitutents, with 2,4-pentanedione **5a** proceeded smoothly, and afforded the corresponding Michael adducts **7a–i** in high yield (up to 94%) with excellent enantioselectivities (up to 97%) (Table 2, entries 1–9). This observation suggests that the nature of the nitroolefins has no significant influence on the enantioselectivities. Meanwhile, a heteroaromatic nitroolefin, such as **6j**, displayed high activity in this reaction. For example, the reaction of **5a** with **6j** furnished **7j** in 96% yield with >99% *ee* (Table 2, entry 10). Furthermore, **5b** reacted with **6a** forming **7l** in 92% yield and 91% *ee*, respectively (entry 12).

Encouraged by these results, the substrate scope of the reaction with several β-keto esters was also investigated (Table 3). As shown in Table 3, in all cases, the Michael adducts were obtained in high yields with predominately the *syn* diastereomer, and good to excellent enantioselectivity. The reaction of β-nitrostyrene (**6a**) and keto esters **8a–c** provided the corresponding products **9a–c** in good yields and enantioselectivities, but the diastereoselectivities were moderate (Table 3, entries 1–3). However, excellent diastereoselectivities (>99:1) and enantioselectivities (>99%) were obtained when cyclic β-keto esters **8d** and **8e** were used in these asymmetric transformations (entries 4–13), which is in sharp contrast to previous

Table 2. Asymmetric Michael addition of 1,3-dicarbonyl compounds **5** with nitroalkenes **6** catalyzed by catalyst **1a**.[a]



5 **6** **7**

5a: R = Me
5b: R = Ph

Entry	5	Nitroolefin 6	Product	Yield [%][b]	*ee* [%][c]
1	**5a**	R^1 = Ph (**6a**)	**7a**	93	97
2	**5a**	R^1 = 4-Me-C_6H_4 (**6b**)	**7b**	87	89
3	**5a**	R^1 = 4-MeO-C_6H_4 (**6c**)	**7c**	89	90
4	**5a**	R^1 = 2-MeO-C_6H_4 (**6d**)	**7d**	83	91
5	**5a**	R^1 = 4-Br-C_6H_4 (**6e**)	**7e**	94	90
6	**5a**	R^1 = 2-Br-C_6H_4 (**6f**)	**7f**	88	93
7	**5a**	R^1 = 4-F-C_6H_4 (**6g**)	**7g**	94	96
8	**5a**	R^1 = 2-Cl-C_6H_4 (**6h**)	**7h**	90	94
9	**5a**	R^1 = 2,4-di-Cl-C_6H_3 (**6i**)	**7i**	87	95
10	**5a**	R^1 = 2-thienyl (**6j**)	**7j**	96	>99
11	**5b**	R^1 = 2-thienyl (**6j**)	**7k**	91	95
12	**5b**	R^1 = Ph (**6a**)	**7l**	92	91

[a] Unless otherwise noted, the reactions were carried out with 0.275 mmol of **5**, 0.25 mmol of **6** in 0.1 mL of CH_2Cl_2 in the presence of 1 mol% of catalyst **1a** for 12–24 h.

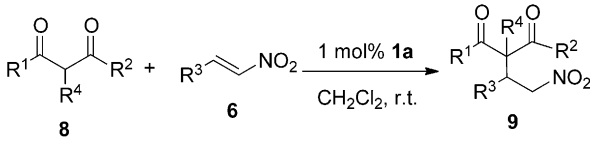
[b] Isolated yield.

[c] Values were determined by HPLC using a chiralpac AD-H column.

results,[6,16] suggesting that the C_3-symmetrical chiral catalyst would likely enhance the enantioselectivity and diastereoselectivity for this asymmetric transformation. For example, the reactions of the keto ester **8e** with nitroolefins **6h** and **6j** were completed within 12 h affording **9l** and **9m** in >99% *dr* with almost one enantiomer only (>99% *ee*) (Table 3, entries 12 and 13). To the best of our knowledge, these results for cyclic keto esters are the best ever achieved. Furthermore, the substituted group at the phenyl ring of nitrostyrene can also be varied without affecting the efficiency of the reaction: 4-methoxynitrostyrene **6c** and 2-chloronitrostyrene **6h** reacted smoothly with **8d** leading to the corresponding products **9e** and **9h** in 99% *dr* and 97% *ee*, respectively (Table 3, entries 5 and 8). Also, we were delightful to find that the heteroaromatic nitroolefin **6k**, bearing a furyl group, reacted with ethyl aceoacetate **8a** to give the desired product **9n** in 93% *ee* (Table 3, entry 14).

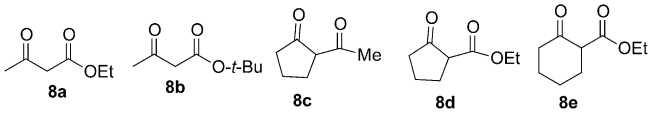
The nice enantioselectivity for heteroaromatic nitroolefins was further demonstrated by the reaction of **6k** with 2-ethoxycarbonycyclohexanone **8e**. Under the optimal conditions, the target compound **9o** was obtained in 84% yield with 95% *ee* of the *syn* diastereomer dominating (*syn*/*anti* = 98:2) (Table 3, entry 15).

Table 3. Variation of nucleophiles in reaction with **6** catalyzed by **1a**.[a]



8 6 9

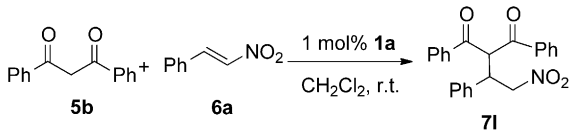
Entry	Keto ester	Nitroolefin	Product	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**8a**	**6a**	**9a**	93	1.2:1	88
2	**8b**	**6a**	**9b**	91	1.3:1	97
3	**8c**	**6a**	**9c**	87	4:1	89
4	**8d**	**6a**	**9d**	93	>99:1	94
5	**8d**	**6c**	**9e**	89	>99:1	97
6	**8d**	**6d**	**9f**	85	>99:1	94
7	**8d**	**6e**	**9g**	95	>99:1	97
8	**8d**	**6h**	**9h**	87	>99:1	97
9	**8d**	**6j**	**9i**	92	>99:1	98
10	**8e**	**6a**	**9j**	92	>99:1	93
11	**8e**	**6e**	**9k**	95	>99:1	95
12	**8e**	**6h**	**9l**	91	>99:1	>99
13	**8e**	**6j**	**9m**	90	>99:1	>99
14	**8a**	**6k**	**9n**	83	1.3:1	93
15	**8e**	**6k**	**9o**	84	98:2	95



8a 8b 8c 8d 8e

[a] Unless otherwise noted, the reactions were carried out with 0.275 mmol of **8**, 0.25 mmol of **6** in 0.1 mL of CH_2Cl_2 in the presence of 1 mol% of catalyst **1a** for 12–24 h.
[b] Isolated yield.
[c] The *syn/anti* ratio was determined by ^{1}H NMR.
[d] Values of *syn*-isomer were determined by HPLC using a chiralpac AD-H or OD-H column.[5f,n]

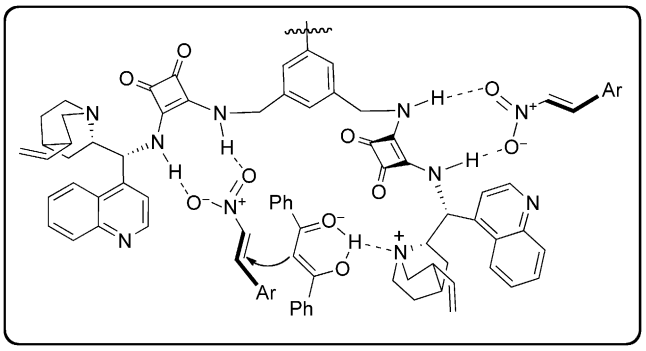
Table 4. Recycling experiments of catalyst **1a** in the Michael addition of **5b** with **6a**.[a]



5b 6a 7l

Cycle no.	Catalyst recovery rate [%]	Yield [%][b]	*ee* [%][c]
1	92	94	91
2	91	93	90
3	89	96	90
4	87	91	91
5	85	93	92
6	83	90	90

[a] All reactions were carried out with 1.1 mmol of **5b**, 1 mmol of **6a**, in 0.5 mL of CH_2Cl_2 in the presence of 1 mol% of catalyst **1a** for 12 h.
[b] Isolated yield.
[c] Values were determined by HPLC using a chiralpac AD-H column.



Scheme 2. Proposed transition state of Michael addition catalyzed by C_3-symmetrical squaramide.

To determine the recyclability of the catalyst, **1a** was recovered after the catalytic process by precipitation from the reaction mixture with the addition of diethyl ether, and then was reused in the Michael addition of **5b** with **6a** under the optimized reaction conditions (Table 4). It is important to note that the catalyst can tolerate recycling, and the recovery rate was up to 83% after six cycles. Meanwhile, we were gratified to observe that the recovered catalyst retained its high activity and high level of enantioselectivity (90–92% *ee*) even after six cycles. This promising advantage will make this approach suitable not only for laboratory-scale research but also for industrial applications.

Based on the observed stereoselectivity, we propose a plausible dual activation model for this Michael addition. The possible transition state for binding of a nitroolefin and a diketone is shown in Scheme 2. First, the scaffold of C_3-symmetrical catalyst was assumed to create three equal reaction sites surrounded by two squaramides,[10c] in which squaramide and cinchonine moiety interacted through hydrogen bonding with nitroolefin and 1,3-diketone simultaneously. The tertiary amine of cinchonine moiety plays the role of the base to deprotonate α-carbon of the carbonyl group, forming the enolate to attack the electrophile. Meanwhile, the two NH groups of the squaramide moiety provide hydrogen bondings to activate the nitro group of the olefin. Since catalyst **1b**, bearing three methyl groups on the phenyl ring, gave sharp decrease in enantioselectivity, this implies that the steric hindrance of the methyl group might disturb this interaction. However, a precise description of the reaction mechanism still requires a more comprehensive mechanistic study.

Conclusions

In summary, we have prepared the new C_3-symmetrical cinchonine-squaramides by simple condensation of a cinchonine-derived amine and diethyl squarate in

two steps with excellent yields. Catalyst **1a**, representative of a new class of C_3-symmetrical bifunctional organocatalyst promoted the asymmetric Michael addition of various 1,3-dicarbonyl compounds to nitroalkenes leading to the respective products in excellent enantioselectivities and diastereoselectivities. Meanwhile, **1a** could be reused for up to six times without a distinct decrease in catalyst activity and enantioselectivity. So far, **1a** is the first example of a highly efficient, and recyclable C_3-symmetrical catalyst for an asymmetric Michael addition reaction. Further investigations to clarify the mechanism and explore applications in other asymmetric transformations are currently underway.

Experimental Section

Unless otherwise noted, reagents and materials were obtained from commercial suppliers and were used without further purification. All solvents were purified according to reported procedures. Reactions were monitored by thin layer chromatography (TLC) and column chromatography purifications were performed using 230–400 mesh silica gel.

Procedure for the Synthesis of 3

To a solution of diethyl squarate (935 mg, 5.5 mmol) in ethanol (10 mL) was added a solution of cinchonine-derived amine (1.465 g, 5 mmol) in ethanol (10 mL) under an N_2 atmosphere. After 12 h, the reaction was completed (as monitored by TLC), then the mixture was concentrated and purified by column chromatography (CH_2Cl_2:CH_3OH = 15:1) to afford the yellow solid **3**; yield: 1.93 g (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, J = 11.7 Hz, 2H), 1.52 (m, 1H), 1.62 (s, 3H), 1.70 (s, 1H), 2.35 (d, J = 7.7 Hz, 1H), 3.00 (m, 5H), 4.06 (br, 2H), 5.15 (d, J = 17.4 Hz, 1H), 5.21 (d, J = 10.3 Hz, 1H), 5.93 (m, 1H), 7.39 (s, 1H), 7.63 (m, 1H), 7.77 (t, J = 7.7 Hz, 1H), 8.17 (m, 2H), 8.92 (d, = 4.4 Hz, 1H).

Representative Procedure for the Synthesis of Catalysts 1a

To a solution of **3** (0.31 mmol) in MeOH (3 mL) was added a solution of 1,3,5-tris-aminomethylbenzene (0.1 mmol) in MeOH (2 mL) under an N_2 atmosphere. After 12 h, the reaction mixture was filtered. The precipitate was rinsed with cold MeOH (3 × 10 mL) to afford the pure catalyst; yiled of **1a**: 83%; yellow solid; mp 255–256 °C; IR (KBr): ν = 3435, 2938, 1797, 1661, 1589, 1536 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.88 (br, 6H), 1.47 (s, 9H), 2.17 (s, 3H), 2.76 (m, 9H), 3.07 (s, 3H), 3.26 (d, J = 8 Hz, 3H), 4.60 (s, 6H), 5.08 (d, J = 12 Hz, 3H), 5.13 (d, J = 16 Hz, 3H), 5.79 (br, 3H), 6.04 (s, 3H), 7.16 (s, 3H), 7.70 (m, 13H), 7.90 (br, 3H), 8.06 (d, J = 8 Hz, 3H), 8.41 (d, J = 4 Hz, 3H), 8.9d (br, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.96, 25.98, 27.22, 38.63, 45.81, 46.66, 48.89, 59.30, 114.51, 119.28, 123.25, 126.31, 126.64, 127.04, 129.43, 129.92, 139.54, 140.51, 145.48, 148.05, 150.37, 166.88, 166.92, 182.09, 182.33; HR-MS: m/z = 1279.6285, calcd. for $C_{78}H_{79}N_{12}O_6$ $(M+H)^+$: 1279.6167.

General Procedure for the Enantioselective Michael Addition Reactions

To a vial with nitroolefin (0.25 mmol) in CH_2Cl_2 (0.1 mL) was added catalyst **1a** (1 mol%, 0.0025 mmol), and the mixture was stirred for 5 min under an N_2 atmosphere. Then 1,3-dicarbonyl compound (0.275 mmol) was added to the mixture. Upon consumption of nitroolefin substrate (monitored by TLC), the reaction mixture was concentrated and purified by column chromatography to afford the conjugate addition product.

Procedure for Recycling of the Catalyst

For the catalyst recycling experiment, dry diethyl ether was added to the reaction mixture after Michael addition until no additional precipitate appeared. Then the mixture was centrifuged and the catalyst deposited at the bottom of the vial. The liquid layer was siphoned out; the residual solid was washed again until no more compounds were detected by TLC. Then the vial with remaining catalyst was dried under vacuum. According to the amount of catalyst, the nitroolefin **6a** and dicarbonyl compound **5b** were then charged for another round of the Michael addition reaction.

Acknowledgements

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References

[1] a) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716; b) L. W. Xu, C. G. Xia, *Eur. J. Org. Chem.* **2005**, 633–639; c) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894; d) J. Christoffers, *Eur. J. Org. Chem.* **1998**, 759–761; e) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033–8061; f) N. Krause, A. Hoffmann-Roder, *Synthesis* **2001**, 171–196; g) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726–1728; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688–1690; h) W. Notz, F. Tanaka, C. F. Barbas, *Acc. Chem. Res.* **2004**, *37*, 580–591; i) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933–971; j) D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; k) J. L. Vicario, D. Badia, L. Carrillo, *Synthesis* **2007**, 2065–2092; l) S. Sulzer-Mosse, A. Alexakis, *Chem. Commun.* **2007**, 3123–3135; m) C. F. Nising, S. Brase, *Chem. Soc. Rev.* **2008**, *37*, 1218–1228.

[2] a) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas, *Org. Lett.* **2004**, *6*, 2527–2530; b) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393–1395; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369–1371; c) N. Mase, K. Watanabe, H. Yoda, K. Takabe et al., *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967.

[3] a) H. B. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171; b) T. Inokuma, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2006**, *128*, 9413–9419; c) C. L. Cao, M. C. Ye, X. L. Sun, Y. Tang, *Org. Lett.* **2006**, *8*, 2901–2904; d) X. X. Jiang, Y. F. Zhang, S. C. A. Chan, R. Wang, *Org. Lett.* **2009**, *11*, 153–156; e) Y. Takemoto, *Chem. Pharm. Bull.* **2010**, *58*, 593–601.

[4] S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599–602.

[5] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; b) B. Tan, X. Zhang, P. J. Chua, G. F. Zhong, *Chem. Commun.* **2009**, 779–781; c) W. M. Zhou, H. Liu, D. M. Du, *Org. Lett.* **2008**, *10*, 2817–2820; d) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; e) H. M. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907; f) J. Wang, H. Li, W. H. Duan, L. S. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713–4716; g) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525–6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370; h) H. M. Li, Y. Wang, L. Tang, F. H. Wu, X. F. Liu, C. Y. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107–110; *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108; i) M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454–1455; j) J. Lubkoll, H. Wennemers, *Angew. Chem.* **2007**, *119*, 6965–6968; *Angew. Chem. Int. Ed.* **2007**, *46*, 6841–6844; k) C. J. Wang, Z. H. Zhang, X. Q. Dong, X. J. Wu, *Chem. Commun.* **2008**, 1431–1433; l) P. Gao, C. G. Wang, Y. Wu, Z. H. Zhou, C. C. Tang, *Eur. J. Org. Chem.* **2008**, 4563–4566; m) J. Luo, L. W. Xu, R. A. S. Hay, Y. X. Lu, *Org. Lett.* **2009**, *11*, 437–440; n) R. Manzano, J. M. Andres, M. D. Muruzabal, R. Pedrosa, *Adv. Synth. Catal.* **2010**, *352*, 3364–3372.

[6] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.

[7] a) C. Moberg, *Angew. Chem.* **2006**, *118*, 4838–4840; *Angew. Chem. Int. Ed.* **2006**, *45*, 4721–4723; b) S. E. Gibson, M. P. Castaldi, *Angew. Chem.* **2006**, *118*, 4834–4837; *Angew. Chem. Int. Ed.* **2006**, *45*, 4718–4720.

[8] a) S. G. Kim, K. H. Kim, J. Jung, S. K. Shin, K. H. Ahn, *J. Am. Chem. Soc.* **2002**, *124*, 591–596; b) K. H. Ahn, H. Y. Ku, Y. Kim, S. G. Kim, Y. K. Kim et al., *Org. Lett.* **2003**, *5*, 1419–1422; c) L. H. Gade, S. Bellemin-Laponnaz, *Chem. Eur. J.* **2008**, *14*, 4142–4152.

[9] a) J. Han, H. Wu, M. Y. Teng, Z. Y. Li, Y. N. Wang, L. Y. Wang, Y. Pan, *Synlett* **2009**, 933–936; b) C. Palomo, M. Oiarbide, R. Lopez, *Chem. Soc. Rev.* **2009**, *38*, 632–653; c) Y. T. Wu, J. S. Siegel, *Chem. Rev.* **2006**, *106*, 4843–4867; d) V. M. Tsefrikas, L. T. Scott, *Chem. Rev.* **2006**, *106*, 4868–4884.

[10] a) S. E. Gibson, M. P. Castaldi, *Chem. Commun.* **2006**, 3045–3062; b) A. Z. Gonzalez, F. D. Toste, *Org. Lett.* **2010**, *12*, 200–203; c) K. Murai, S. Fukushima, S. Hayashi, Y. Takahara, H. Fujioka, *Org. Lett.* **2010**, *12*, 964–966; d) D. M. Du, T. Fang, J. X. Xu, S. W. Zhang, *Org. Lett.* **2006**, *8*, 1327–1330; e) J. Zhou, Y. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 9030–9031; f) M. C. Ye, J. Zhou, Y. Tang, *J. Org. Chem.* **2006**, *71*, 3576–3582; g) J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2005**, *34*, 664–676; h) P. D. Cao, Y. Y. Zhou, X. L. Sun, J. C. Zheng, Z. W. Xie, Y. Tang, *Angew. Chem.* **2010**, *122*, 4565–4558; *Angew. Chem. Int. Ed.* **2010**, *49*, 4463–4466.

[11] M. T. Reetz, H. C. Guo, J. A. Ma, R. Goddard, R. J. Mynott, *J. Am. Chem. Soc.* **2009**, *131*, 4136–4142.

[12] a) T. Shinada, T. Isida, Y. Ohfune, *J. Synth. Org. Chem. Jpn.* **2007**, *65*, 30–43; b) L. A. Hall, D. J. Williams, *Adv. Inorg. Chem.* **2001**, *52*, 249–291.

[13] a) L. Dai, S. X. Wang, F. E. Chen, *Adv. Synth. Catal.* **2010**, *352*, 2137–2141; b) H. Konishi, T. Y. Lam, J. P. Malerich, V. H. Rawal, *Org. Lett.* **2010**, *12*, 2028–2031; c) Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem.* **2010**, *122*, 157–160; *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156; d) J. W. Lee, T. H. Rhu, J. S. Oh, H. Y. Bae, H. B. Jang, C. E. Song, *Chem. Commun.* **2009**, 7224–7226; e) W. Yang, D. M. Du, *Org. Lett.* **2010**, *12*, 5450–5453.

[14] For our work in applying squaric acid derivatives in asymmetric catalysis, see: a) H. B. Zhou, S. M. Lu, R. G. Xie, A. S. C. Chan, T. K. Yang, *Tetrahedron Lett.* **2001**, *42*, 1107–1110; b) H. B. Zhou, S. M. Lu, R. G. Xie, Z. Y. Zhou, M. C. K. Choi, A. S. C. Chan, T. K. Yang, *Tetrahedron* **2001**, *57*, 9325–9333; c) S. M. Lu, H. B. Zhou, R. G. Xie, Z. Y. Zhou, A. S. C. Chan, T. K. Yang, *Acta Chim. Sinica* **2001**, *59*, 587–593; d) J. Zhang, H. B. Zhou, S. M. Lu, M. M. Luo, R. G. Xie, M. C. K. Choi, Z. Y. Zhou, A. S. C. Chan, T. K. Yang, *Tetrahedron: Asymmetry* **2001**, *12*, 1907–1912; e) X. Q. Jin, Q. Q. Min, Y. F. Zheng, P. C. Wang, J. Zhu, H. B. Zhou, *ARKIVOC*, **2010**, *xi*, 322–335.

[15] Bisquaramide and monosquaramide were also prepared for comparison. Both gave inferior enantioselectivity. See the Supporting Informations for details.

[16] T. H. Y. Okino, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125.

