

Novel bifunctional chiral squaramide-amine catalysts for highly enantioselective addition of mono- and diketones to nitroalkenes

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Abstract

Novel bifunctional chiral squaramide–amine organocatalysts have been developed by rational combination of pyrrolidine and a cinchona alkaloid. The catalysts promoted the enantioselective Michael addition of both mono- and diketones to a broad range of nitroalkenes providing the corresponding products in moderate to high yields with excellent enantioselectivities and diastereoselectivities (up to 96% yield, 96% ee, 98:2 *dr*) under mild conditions. These results demonstrate that the assembly of two chiral privileged skeletons, pyrrolidine and cinchonine with a squaramide linker is a useful strategy to reach a wider substrate scope, high reaction efficiency and enantioselectivity. The match of the chiralities between two backbones embedded in the catalysts is also critical for improving enantioselectivity.

Keywords: Chiral squaramide–amine, organocatalyst, asymmetric Michael addition, pyrrolidine, cinchonine

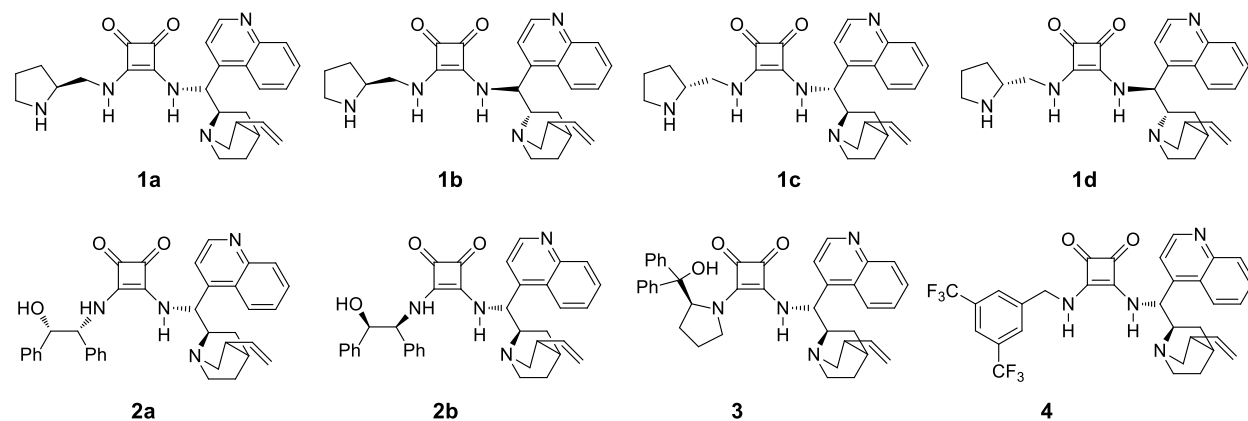
Introduction

In the past decade, the organocatalytic asymmetric Michael reaction has emerged as one of the most important carbon-carbon bond forming reactions in organic chemistry.¹ In particular, the conjugate addition of ketones to nitroolefins has received extensive attention since the resulting nitroalkanes are versatile intermediates, in which the nitro group can be transformed into various useful functional groups.² Stimulated by the seminal works of List, Barbas and co-workers,³ several research groups focused on the development of more efficient primary,⁴ secondary,⁵ amine-based catalysts and also thioureas, in order to both improve the selectivity and substrate scope.⁶ The development of multifunctional chiral organocatalysts is of great importance.⁷ In

2006, the Jacobsen group successfully applied bifunctional thiourea catalysts to Michael addition and achieved good results.⁸ Recently, the Xiao group developed new thiourea-amine organocatalysts by combining two privileged backbones into one, in the generation of highly efficient catalysts for Michael reaction.⁹ Despite the progress in this area, the existing catalytic systems are still limited. Therefore, new strategies to design more efficient chiral catalysts for this type of reaction are highly desirable.

In addition, squaramides have been studied in molecular recognition,¹⁰ supramolecular assemblies,¹¹ and chiral organocatalysts for asymmetric transformations.¹² It is known that these molecules also exhibit a dual donor–acceptor hydrogen bonding ability. Due to its unique structure feature and wide application, squaramide still has great potential to explore in asymmetric catalysis. To the best of our knowledge, there is no report on the development of new squaramide-amine bifunctional catalysts by combination of two backbones, which are connected by a squaramide motif. In continuation of our interest in developing new squaramides that are of potential in asymmetric catalysis,¹³ we envisioned that the assembly of two privileged frameworks with a squaramide linker would constitute a new class of bifunctional organocatalysts, and the well-defined, rigid, bifunctional squaramide would serve as an efficient stereocontrol element for asymmetric Michael reaction. Herein, we describe the synthesis of unprecedented squaramide-amine bifunctional catalysts by rational incorporation of structurally privileged pyrrolidine,¹⁴ and cinchona alkaloids,¹⁵ into one molecule.

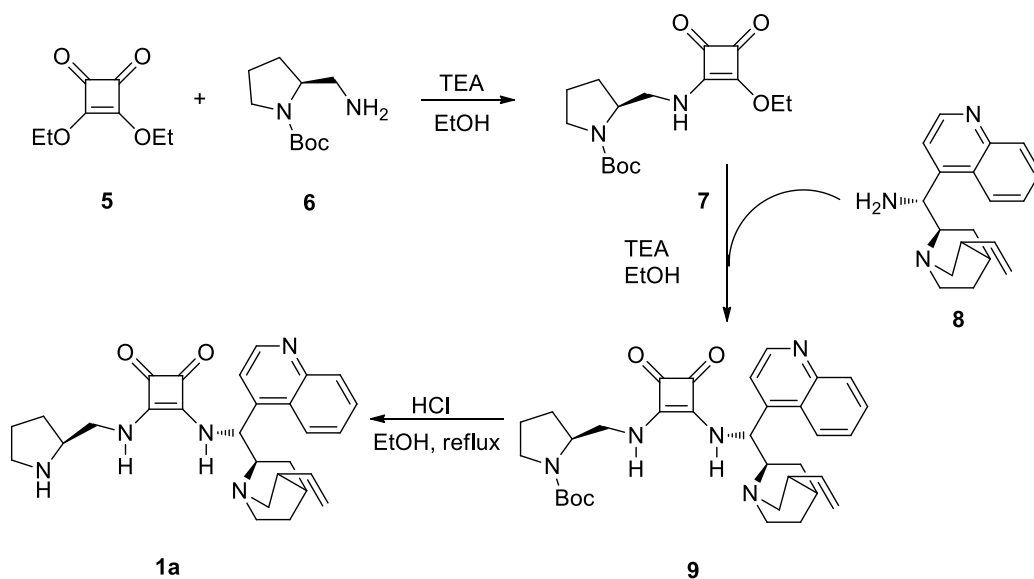
The pyrrolidine structural unit can also be replaced with appropriate functionalities, such as 3,5-bis(trifluoromethyl)benzylamine,¹² 2-amino-1,2-diphenyl-ethanol and prolinol,¹⁶ as illustrated in Scheme 1. These squaramide bifunctional catalysts proved to be highly efficient for Michael addition of both mono- and diketones to a broad range of nitroalkenes, affording the products in high yields with excellent enantioselectivities and diastereoselectivities.



Scheme 1. New class of bifunctional chiral squaramide–amine catalysts **1-3** and previously reported catalyst **4**.

Results and Discussion

A series of squaramide-based catalysts (Scheme 1) were prepared and applied to enantioselective Michael addition reactions. The catalysts were easily synthesized by sequential addition–elimination reactions of two amines with diethyl squarate **5** (3,4-diethoxy-3-cyclobutene-1,2-dione). The synthetic procedure is illustrated in Scheme 2. Treatment of (*S*)-2-aminomethyl-1-*N*-Boc-pyrrolidine **6** with one equivalent of diethyl squarate **5** in the presence of triethylamine in ethanol at room temperature gave the corresponding squaric monoamide monoester **7** in 87% yield. Subsequently, the reaction of **7** with the cinchonine-derived amine **8** under the same reaction conditions afforded the Boc-protected squaramide-amine **9** (73%), which was then deprotected directly with HCl to give the desired organocatalyst **1a** in 88% yield. Other squaramide-amine catalysts **1b-d**, **2** and **3** were synthesized by a similar procedure. The structures of the catalysts **1-3** were fully characterized (see the Supporting Information).



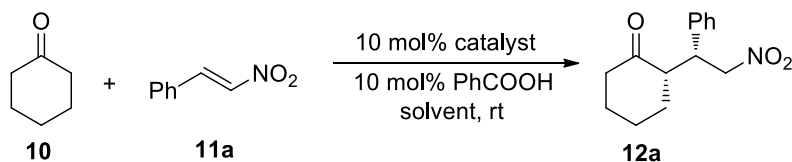
Scheme 2. Synthetic route for catalyst **1a**.

Initially, the Michael addition of a monoketone was investigated. A brief survey of reaction conditions was carried out for the reaction of cyclohexanone **10** with *trans*-nitrostyrene **11a** using **1a** as catalyst (Table 1). We found that the solvent, catalyst loading, and acid additive are critical determinants of the reaction efficiency. Ultimately, we found that the use of 10 mol% **1a** and 10 mol% of PhCO₂H in THF is the preferred catalyst system for achieving good yield and high enantioselectivity (Table 1, entry 4). Reducing or enhancing the catalyst loading did not benefit the enantioselectivity at all. It is noteworthy that the reaction proceeded much more slowly and only trace amount of the product was observed in the absence of PhCO₂H (Table 1, entry 11). Other substituted benzoic acids such as *o*-nitrobenzoic acid, *p*-bromobenzoic acid, *p*-

methylbenzoic acid, and TFA gave the product in lower diastereoselectivity or enantioselectivity. The result indicated that the nitrogen atom of the cinchonine as well as the benzoic acid may orientate the nitro group through a hydrogen bonding interaction, so that the cyclohexanone pyrrolidine enamine attacks the nitroalkene as a nucleophile from a specific face to give the high enantio- and diastereoselectivity. So in all the reactions investigated, 10 mol% of PhCO₂H was used as additive.

The effectiveness of several related chiral squaramides was also evaluated. As shown in Table 1, the combinations of the pyrrolidine with a cinchona alkaloid do indeed play an important role in the stereocontrol in this Michael addition. For chiral squaramide-amine **1a**, derived from L-proline and cinchonine, in the addition of cyclohexanone **10** to nitrostyrene **11a**, always displayed higher selectivity. However, when cinchonidine was incorporated into the catalyst backbone (catalyst **1b**), both the yield and enantioselectivity of Michael adduct decreased (Table 1, entries 1 vs 12). For catalyst **1c**, which was prepared from D-proline and cinchonine, inferior results were observed (entry 13). The catalyst **1d**, derived from the D-proline and cinchonidine, induced higher enantioselectivity than those of **1b-c**, the opposite enantiomeric product was generated in 52% yield and 68% ee, respectively (entry 14). In contrast, catalysts **2** and **3**, which possess 2-amino-1,2-diphenylethanol and prolinol moieties, gave no product in this reaction. Surprisingly, the known catalyst **4**,^{12a} which exhibits excellent enantioselectivity in catalyzing Michael reaction of diketones and nitroalkenes, showed no activity in conjugate addition of cyclohexanone **10** to nitrostyrene **11a** (Table 1, entry 18). These results demonstrated that the presence of two chiral privileged skeletons, pyrrolidine and cinchonine, with a squaramide linker improve the performance of the catalyst, which is a useful strategy to reach a wider substrate scope, high reaction efficiency and enantioselectivity, justifying the design concept.

Table 1. Optimization and catalyst screening for Michael addition of cyclohexanone **10** with nitrostyrene **11a**^a



Entry	Cat.	Solvent	Yield (%) ^{b,c}	ee (%) ^d
1	1a	toluene	56 (96:4)	74
2	1a	CH ₂ Cl ₂	30 (96:4)	93
3	1a	MeOH	NR	
4	1a	THF	60 (88:12)	93
5 ^e	1a	THF	Traces	ND
6	1a	CH ₃ CN	28 (88:12)	85

Table 1. Continued

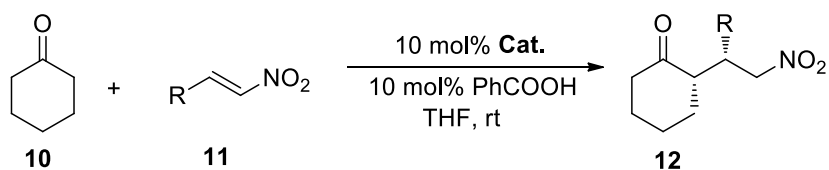
Entry	Cat.	Solvent	Yield (%) ^{b,c}	ee (%) ^d
7	1a	1,4-dioxane	31 (93:7)	9
8	1a	<i>n</i> -hexane	42 (97:3)	74
9	1a	DMF	NR	
10	1a	neat	68 (90:10)	66
11 ^f	1a	toluene	traces	
12	1b	toluene	44 (92:8)	59
13	1c	toluene	50 (90:10)	58 ^g
14	1d	toluene	52 (90:10)	68 ^g
15	2a	toluene	NR	
16	2b	toluene	NR	
17	3	toluene	NR	
18	4	toluene	NR	

^aUnless otherwise noted, the reactions were carried out with 0.2 mmol of **1a**, 2.0 mmol of cyclohexanone **10** in the presence of 10 mol% of catalyst **1a** and 10 mol% of PhCO₂H, in 1.0 mL of solvent indicated, for 48 h, ^bIsolated yield for both diastereomers, ^cNumbers in parenthesis correspond to the *syn/anti* ratio determined by ¹H NMR spectroscopy, ^dEnantiomeric excess of major diastereoisomer, determined by HPLC on AD-H chiral column, ^eReaction conducted using 5 mol% of **1a**, ^fReaction conducted in the absence of PhCO₂H. ^gOpposite configuration was observed.

Having optimized the reaction conditions, we next investigated the scope of chiral squaramide catalyzed enantioselective Michael reaction of cyclohexanone with a variety of nitroolefins and the results are shown in Table 2. In addition to cyclohexanone **10**, various nitroolefin derivatives with different substitution patterns on the aromatic ring in the presence of 10 mol% of **1a** with 10 mol% of PhCO₂H as the cocatalyst, gave the corresponding Michael adducts **12a–j** with excellent diastereoselectivities (up to 98/2 *dr*) and enantioselectivities (up to 93% ee) (Table 2, entries 1–10). However, the yields varied dramatically and no clear trend was observed with regard to the substituent on the aromatic ring. When aryl nitroolefins containing electron-withdrawing or electron-donating substituents on the aromatic ring (i.e. **11b–d**, **11f**, **11i** and **11j**) were used for the reaction with **10**, the reactions proceeded smoothly resulting in the formation of products in good yields (72–84%, Table 2, entries 2–4, 6, 9 and 10). However, aryl nitroolefins **11e**, **11g**, and **11h**, bearing 2-chloro, 4-trifluoro and 3-nitro groups, respectively, were exceptional, giving the products in only low to moderate yields (41–60%, Table 2, entries 5, 7 and 8). Phenyl nitroolefin **11a** without a substituent afforded the product in 60% yield (Table 2, entry 1). Heteroaromatic nitroolefins, such as 2-thienyl nitroolefin **11i**, gave a 75% of ee (Table

2, entry 12). 2-Furyl nitroolefin **11k**, gave the product in 70% yield with 80/20 dr and 81% ee (Table 2, entry 11). Other catalysts, such as **1d**, proved to be effective providing the products with opposite configuration in reasonable yields and good ee values (entries 13 and 14). Aliphatic nitroolefins displayed much less reactivity in this reaction, for example, when (*E*)-1-nitropent-1-ene **11n** was used, only trace amount of product was observed (Table 2, entry 15).

Table 2. Evaluation of the scope of the Michael addition of cyclohexanone **10** and nitroalken **11**^a.



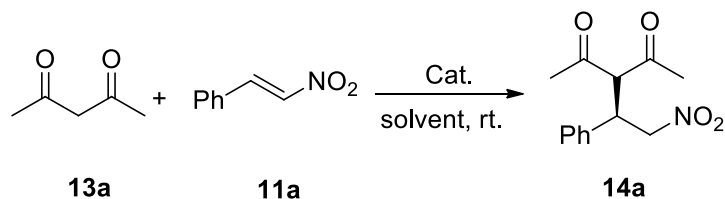
Entry	Nitroolefin	Cat.	Product	Yield (%) ^{b, c}	ee (%) ^d
1	R = Ph (11a)	1a	12a	60 (88:12)	93
2	R = 4-F-C ₆ H ₄ (11b)	1a	12b	81 (86:14)	82
3	R = 4-Br-C ₆ H ₄ (11c)	1a	12c	80 (87:13)	83
4	R = 2-Br-C ₆ H ₄ (11d)	1a	12d	84 (97:3)	84
5	R = 2-Cl-C ₆ H ₄ (11e)	1a	12e	60 (98:2)	93
6	R = 2,4-Cl ₂ -C ₆ H ₃ (11f)	1a	12f	80 (80:20)	85
7	R = 4-CF ₃ -C ₆ H ₄ (11g)	1a	12g	41 (88:12)	80
8	R = 3-NO ₂ -C ₆ H ₄ (11h)	1a	12h	50 (86:14)	86
9	R = 2-MeO-C ₆ H ₄ (11i)	1a	12i	74 (97:3)	81
10	R = 4-Me-C ₆ H ₄ (11j)	1a	12j	72 (83:7)	80
11	R = 2-Furyl (11k)	1a	12k	70 (80:20)	81
12	R = 2-Thienyl (11l)	1a	12l	71 (83:7)	75
13	R = Ph (11a)	1d	12a	60 (90:10)	86 ^e
14	R = 2-Cl-C ₆ H ₄ (11e)	1d	12e	55 (96:4)	92 ^e
15	R = <i>n</i> -propyl (11n)	1a	12m	Trace	ND

^aUnless otherwise noted, the reactions were carried out with 0.2 mmol of **11**, 2.0 mmol of cyclohexanone **10** in 1.0 mL of THF in the presence of 10 mol% of catalyst **1a** and 10 mol% of PhCO₂H for 48 h. ^bIsolated yield for both diastereoisomers, ^cNumbers in parenthesis correspond to the *syn/anti* ratio determined by ¹H NMR, ^dEnantiomeric excess of major diastereoisomer, determined by chiral HPLC, ^eOpposite configuration was observed.

Besides monoketone **10**, the catalytic effect of the bifunctional squaramides catalysts in Michael addition of diketones was also evaluated. After a brief optimization of reaction

conditions, we found that CH₂Cl₂ was preferred as solvent with 1 mol% catalyst **1a** (Table 3, entry 7). Other solvents, e.g. toluene, THF, *n*-hexane, methanol, *etc* were also investigated, however, none of them gave better results (Table 3, entries 2-5). Neither reducing the catalyst loading from 1 to 0.5 mol% (Table 3, entry 6) nor enhancing the catalyst loading to 2, 5, even 10 mol% (Table 3, entries 1-8 and 9) benefited the enantioselectivity.

Table 3. Optimization of reaction conditions of the Michael addition of 2, 4-pentanedione **13a** with nitrostyrene **11a**^a



Entry	Cat.	Solvent	Cat. (mol%)	Time (h)	Yield (%) ^b	ee (%) ^c
1	1a	CH ₂ Cl ₂	10	12	94	87
2	1a	toluene	10	12	83	76
3	1a	THF	10	12	71	83
4	1a	<i>n</i> -Hexane	10	12	67	73
5	1a	MeOH	10	20	60	63
6	1a	CH ₂ Cl ₂	0.5	20	94	86
7	1a	CH ₂ Cl ₂	1	12	96	93
8	1a	CH ₂ Cl ₂	2	12	96	89
9	1a	CH ₂ Cl ₂	5	12	97	87
10	1b	CH ₂ Cl ₂	1	12	86	82 ^d
11	1c	CH ₂ Cl ₂	1	12	8	85
12	1d	CH ₂ Cl ₂	1	12	93	87 ^d
13	2a	CH ₂ Cl ₂	1	12	93	12
14	2b	CH ₂ Cl ₂	1	12	90	60
15	3	CH ₂ Cl ₂	1	12	92	77

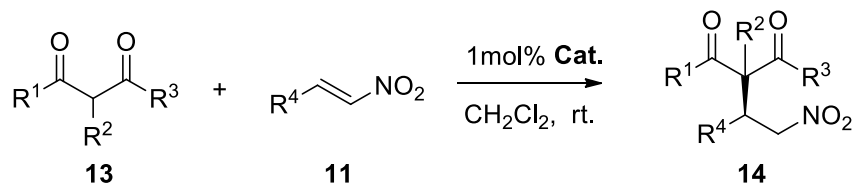
^aThe reactions were carried out with 0.5 mmol of **11a**, 1.0 mmol of 2,4-pentanedione **13a** in the presence of specific amount of catalyst **1a**, in 1.0 mL of solvent indicated for 12-20 h. ^bIsolated yield, ^cDetermined by chiral HPLC. ^dOpposite configuration was observed.

The optimized conditions were then used to assess the activity of other chiral squaramides **1b-d**, **2** and **3**. As in the Michael additions of a monoketone, the combination of the pyrrolidine with cinchona alkaloid proved critical for this Michael addition. Again the chiral squaramide-amine **1a**, derived from L-proline and cinchonine, displayed higher selectivity; while the catalyst

1b, possessing a cinchonidine backbone, was less effective, giving the product with opposite configuration in 86% yield and 82% ee, respectively (Table 3, entry 10). A lower yield but good enantioselectivity was observed when **1c** was used in this reaction, which prepared from D-proline and cinchonine (entry 11). Furthermore, catalyst **1d**, derived from D-proline and cinchonidine, induced higher enantioselectivity than **1b-c**, giving the desired product in 93% yield and 87% ee (entry 12). These results demonstrated the significance of matching the chiralities of the two backbones embedded in the catalysts on the reactivity and enantioselectivity. Lastly, two catalysts having the core structure of cinchonine-substituted squaramide but differing in the pyrrolidine moiety were examined, for example **2** and **3**, and all were found to provide the product in good yield but lower ee value (Table 3, entries 13-15).

With the optimal reaction conditions in hand, we next examined other nitroolefins and 1,3-dicarbonyl compounds to expand the substrate scope of catalyst **1a**, and the results are shown in Table 4. Various electron-poor and electron-rich nitroolefins with various substitution patterns on the aromatic ring reacted smoothly with 2,4-pentanedione **13a** in the presence of 1 mol% of **1a**, giving the corresponding Michael adducts **14a-h** in high to excellent yields (88–96%), with high enantioselectivities (81–96% ee) (Table 4, entries 1–8), including the heteroaromatic nitroolefin, such as **11i**, afforded the product in 83% ee (Table 4, entry 7).

Table 4. Variation of electrophile and nucleophile in the Michael addition of 2,4-pentanediones **13** with nitroalkenes **11**^a



Entry	1,3-Dicarbonyl compound	Nitroolefin	Cat.	Prod uct	yield (%) ^{b,c}	ee (%) ^d
1	R ¹ = R ³ = Me, R ² = H 13a	R ⁴ = Ph 11a	1a	14a	96	93
2	R ¹ = R ³ = Me, R ² = H 13a	R ⁴ = 4-F-C ₆ H ₄ 11b	1a	14b	88	88
3	R ¹ = R ³ = Me, R ² = H 13a	R ⁴ = 4-Br-C ₆ H ₄ 11c	1a	14c	92	81
4	R ¹ = R ³ = Me, R ² = H 13a	R ⁴ = 2-Br-C ₆ H ₄ 11d	1a	14d	90	92
5	R ¹ = R ³ = Me, R ² = H 13a	R ⁴ = 4-Me-C ₆ H ₄ 11j	1a	14e	91	88

Table 4. Continued

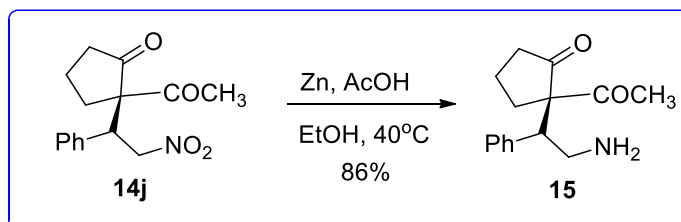
Entry	1,3-Dicarbonyl compound	Nitroolefin	Cat.	Prod uct	yield (%) ^{b,c}	ee (%) ^d
6	R ¹ = R ³ = Me, R ² = H 13a	R ⁴ = 2-Furyl 11k	1a	14f	90	73
7	R ¹ = R ³ = Me, R ² = H 13a	R ⁴ = 2-Thienyl 11l	1a	14g	89	83
8	R ¹ = R ³ = Me, R ² = H 13a	R ⁴ = 4-MeO-C ₆ H ₄ 11m	1a	14h	92	96
9	R ¹ = Ph, R ² = H, R ³ = OEt 13b	R ⁴ = Ph 11a	1a	14i	90 (1:1)	85/84
10	R ¹ , R ² = -(CH ₂) ₃ -, R ³ = Me 13c	R ⁴ = Ph 11a	1a	14j	81 (1:1)	88/86
11	R ¹ , R ² = -(CH ₂) ₃ -, R ³ = OEt 13d	R ⁴ = Ph 11a	1a	14k	85 (24:1)	83/87
12	R ¹ = Me, R ² = H, R ³ = OMe 13e	R ⁴ = Ph 11a	1a	14l	92 (1.1:1)	86/80
13	R ¹ = Me, R ² = H, R ³ = OEt 13f	R ⁴ = Ph 11a	1a	14m	91 (1.1:1)	87/86
14	R ¹ = Me, R ² = H, R ³ = OtBu 13g	R ⁴ = Ph 11a	1a	14n	86 (12:1)	86/86
15	R ¹ = Et, R ² = H, R ³ = OMe 13h	R ⁴ = Ph 11a	1a	14o	90 (1:1)	86/80
16	R ¹ = R ³ = Me, R ² = H 13a	R ⁴ = Ph 11a	1d	14a	89	87 ^e
17	R ¹ = R ³ = Me, R ² = H 13a	R ⁴ = 4-MeO-C ₆ H ₄ 11m	1d	14h	92	92 ^e

^aUnless otherwise noted, the reactions were carried out with 0.2 mmol of **11**, 0.4 mmol of **13** in 1.0 mL of CH₂Cl₂ in the presence of 1 mol% of catalyst **1a** for 12-36h. ^bIsolated yield; ^cNumbers in parenthesis correspond to the *syn/anti* ratio determined by ¹H NMR. ^dValues are listed for major and minor diastereomers, respectively, and are determined by HPLC. ^eOpposite configuration was observed.

When comes to other 1,3-dicarbonyl compounds **13b-h**, in the reaction with **11a**, all reactions proceeded in good to excellent yields and, generally, good enantioselectivities (Table 4, entries 9-15). Although several of the reactions proceeded with lower diastereoselectivity, each of the diastereomers was formed in very good enantioselectivity. As expected, employment of

catalyst **1d** led to high selectivity and enantioselectivity and opposite configuration was observed (Table 4, entries 16 and 17).

In addition, we also investigated the use of these nitroalkanes as starting materials for further transformation. For example, as shown in Scheme 3, in the presence of zinc in acetic acid, **14j** was smoothly reduced to corresponding amine **15** in 86% yield.



Scheme 3. Further transformation of the Michael adduct.

Conclusions

In conclusion, we have designed a new class of bifunctional chiral squaramide–amine catalysts by a rational combination of readily available pyrrolidines with cinchona alkaloids. The catalyst **1a** exhibited the best performance in the asymmetric addition of both mono- and diketones to a broad range of nitroalkenes. The corresponding products can be obtained in moderate to high yields with excellent enantioselectivities and diastereoselectivities under mild conditions. The match of the chiralities between two backbones embedded in catalysts is also critical for improving enantioselectivity.

Experimental Section

General. Tetrahydrofuran, diethyl ether and toluene were dried over Na/benzophenone, dichloromethane was dried over CaH₂ and distilled prior to use. Reaction progress was monitored using analytical thin-layer chromatography (TLC) on 0.25 mm Merck F-254 silica gel glass plates. Visualization was achieved by UV light (254 nm). Flash chromatography was performed with silica gel (Merck, 230-400 mesh). Unless otherwise noted, all NMR spectra were recorded using CDCl₃ as the solvent with reference to residual CHCl₃ (¹H at 7.24 ppm and, ¹³C at 77.0 ppm). Optical rotations were measured at room temperature on a Perkin–Elmer 241MC automatic polarimeter (concentration in g/100 mL). Melting points were obtained on a micro-melting apparatus and the data were uncorrected. Determination of % ee was achieved using a chiral HPLC equipped with a chiralpak AD or OD column with *n*-hexanes: 2-propanol as the mobile phase at a flow rate of 1 mL/min.

Procedure for the preparation of catalyst (1a)

To a solution of diethyl squarate **5** (0.1 mmol) in EtOH (5 mL) with TEA was added (*S*)-2-amino-1-*N*-Boc-pyrrolidine **6** (0.11 mmol) EtOH (5 mL) at room temperature. The reaction mixture was stirred overnight and subjected to column chromatography to afford **7** (87%). To a solution of **7** (0.1 mmol) and amine **8** (0.12 mmol) in EtOH (10 mL) was added TEA (0.1 mmol). After 36 h, the reaction mixture was concentrated and subjected to column chromatography to afford squaramide **9**. The squaramide **9** was dissolved in a mixture of HCl/EtOH (12 mL/60 mL) and stirred for 12 h. The mixture was basified with concentrated ammonia solution and extracted with CH₂Cl₂ (2×40 mL). After the removal of the solvent in vacuum, the residue was purified through flash column chromatography on silica gel (eluent: methanol / TEA = 10:1) giving **1a** as a white solid in 88% yield.¹H NMR (400 MHz, CDCl₃) δ = 0.80-1.87 (m, 9H), 2.10-3.95 (m, 13H), 5.01-5.11 (m, 2H), 5.72-5.80 (m, 1H), 6.25 (s, br, 1H), 7.57-8.79 (m, 6H) ppm, ¹³C NMR (100 MHz, CDCl₃) δ: 183.7, 182.5, 167.9, 150.4, 150.2, 148.8, 147.2, 140.0, 130.4, 129.9, 127.6, 127.1, 124.0, 119.5, 115.4, 60.5, 49.7, 46.6, 45.5, 44.8, 39.3, 29.8, 28.5, 27.9, 26.7, 25.7, 24.2. HRMS (ESI) calcd for C₂₈H₃₃N₅O₂H [M + H]⁺ 472.2713; found 472.2703.

Representative procedure for the asymmetric Michael reaction of nitroolefin (11a) with cyclohexanone (10)

The organocatalyst **1a** (0.05 mmol), PhCO₂H (0.05 mmol) and cyclohexanone **10** (5.0 mmol) were stirred in 2 mL of THF for 10 min at room temperature. β-nitrostyrene **11a** (0.5 mmol) was then added and the reaction mixture was stirred for 48 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate (6:1)) to give the corresponding pure Michael product **12a** (60%) as a white solid.¹H NMR (400 MHz, CDCl₃) δ = 7.36–7.23 (m, 3H), 7.18–7.15 (m, 2H), 4.94 (dd, *J* = 12.5, 4.5 Hz, 1H), 4.64 (dd, *J* = 12.5, 9.9 Hz, 1H), 3.76 (td, *J* = 9.9, 4.5 Hz, 1H), 2.74–2.64 (m, 1H), 2.54–2.33 (m, 2H), 2.13–2.02 (m, 1H), 1.83–1.63 (m, 3H), 1.58–1.48 (m, 1H), 1.33–1.13 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ □ 212.0, 137.9, 129.2, 128.4, 128.1, 79.1, 52.8, 44.2, 43.0, 33.5, 28.6, 25.2. The ee was determined by HPLC using Chiralpak AD column with 10% *i*-PrOH in hexane and the detector set at 220 nm.

General procedure for the asymmetric Michael reaction of nitroolefin (11) with diketones (13)

To a solution of nitroolefin **11** (0.5 mmol) in CH₂Cl₂ (2.0 mL) was added catalyst **1a** (0.005 mmol) and 1,3-dicarbonyl compound **13** (5.0 mmol). Upon consumption of nitroolefin substrate (monitored by TLC), the reaction mixture was concentrated and purified by column chromatography to afford the conjugate addition product **14**.

Supplementary Material

Representative procedures for preparation of catalysts; the procedure for the enantioselective Michael addition of ketones and nitroolefins; spectroscopic data of ligands **1-3**; products **12a-l**, **14a-l**, and representative HPLC spectra of products **12** and **14**.

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