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Modular Bifunctional Chiral Thioureas as Versatile Organocatalysts for Highly Enantioselective Aza-Henry Reaction and Michael Addition

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Abstract: A series of new modular bifunctional chiral thiourea organocatalysts were synthesized from natural *Cinchona* alkaloids and amino acids, and their performance in the aza-Henry reaction of nitroalkanes to imines, the Michael addition of acetylacetone to nitroolefins and the Michael addition of acetone to nitroolefins was investigated. Under the mild conditions, the important building blocks β-nitro amines and γ-nitro carbonyl compounds could be obtained in good yields (up to 95%) with excellent enantioselectivities (up to 99% *ee*) and diastereoselectivity (up to 17:1).

Keywords: asymmetric catalysis; aza-Henry reaction; C–C bond formation; Michael addition; organic catalysis

Introduction

With the development of a chiral pharmaceutical industry, the growing demands in high-throughput screening for enantiomerically pure, biologically active compounds have stimulated the rapid development of enantioselective synthetic methods providing exceptional stereocontrol. Although, during the last two decades, asymmetric catalysis has experienced an explosive growth, and many transformations demonstrating excellent steroselectivities and enantioselectivities have been reported, the design and synthesis of versatile catalysts which can be successfully used in a variety of transformations is still very challenging and in great demand.[1]

Organocatalysis has emerged as one of the most rapidly growing and promising areas in synthetic organic chemistry. The advantages of organocatalysis include their operational simplicity, ready availability, low cost, and low toxicity, which confers a huge direct benefit in the production of pharmaceutical intermediates.[2] Currently, the strategies for organocatalysis include: forming temporary covalent bonds (enamine or iminium catalysis), hydrogen-bonding interactions (urea or the thiourea catalysis), pi-stacking, Brønsted acid-base interactions and ion pair interactions (phase-transfer catalysts), etc.[3] The combination of some of these strategies may lead to an unexpected synergistic effect, and the success of bifunctional organocatalysts in a wide array of asymmetric processes provides a good example.[4] Among the different skeletons of chiral promoters available nowadays, both *Cinchona* alkaloids and amino acid derivatives, which could be easily reduced to β-amino alcohols, are regarded as "privileged" scaffolds in asymmetric catalysis.[5] We envisaged that the rational combination of these two "privileged" structure motifs into one molecule by the linker of thioureas would probably provide a new class of bifunctional organocatalyst, which has the potential to produce an unexpected synergistic effect in many asymmetric transformations.

Herein a series of new modular bifunctional organocatalysts **1a–1h** (Figure 1) was synthesized starting from natural *Cinchona* alkaloids and amino acids with simple procedures. Their catalytic performance was

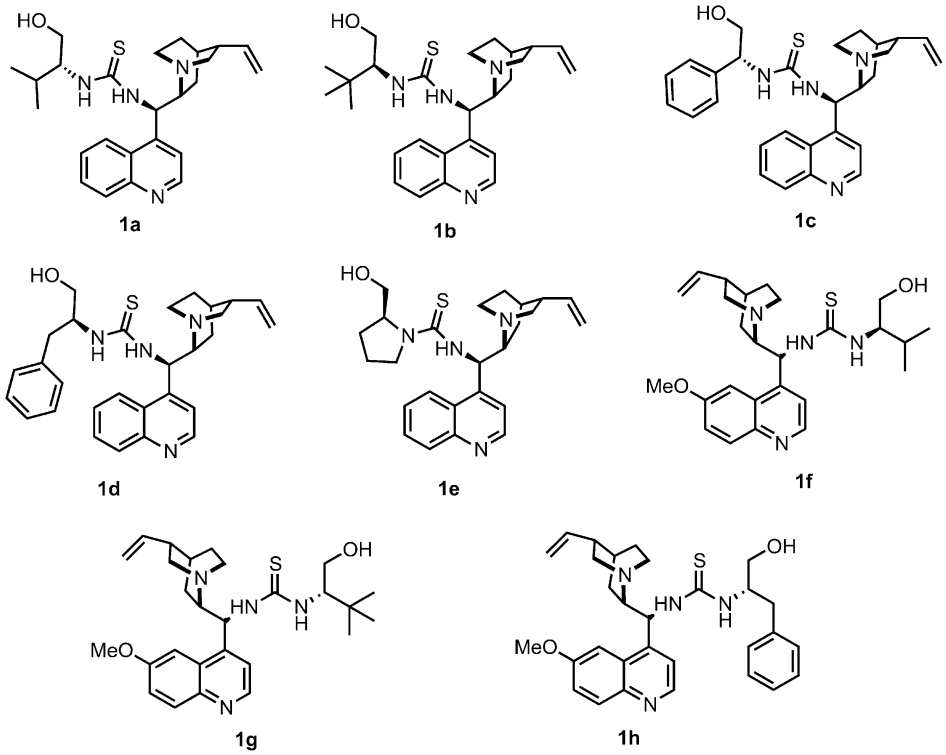


Figure 1. Bifunctional organocatalysts **1a**–**1h** derived from *Cinchona* alkaloids and amino acids.

investigated in the aza-Henry reaction of nitroalkanes to imines, the Michael addition of acetylacetone to nitroolefins and the Michael addition of acetone to nitroolefins. Under the mild conditions, a variety of important building blocks such as β-nitro amines and γ-nitro carbonyl compounds could be prepared in good yields (up to 95%) with excellent enantioselectivities (up to 99% *ee*) and diastereoselectivities (up to 17:1).

Results and Discussion

Aza-Henry Reaction

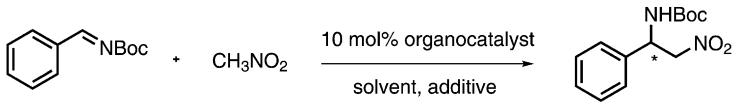
The aza-Henry reaction (or nitro-Mannich reaction), the nucleophilic addition of nitroalkanes to imines, is one of the most important reactions in organic synthesis, which opens useful ways to create a carbon-carbon bond with concomitant generation of two vicinal stereogenic centers bearing nitro and amino functional groups. In recent years, several organocatalysts such as bisamidine-triflate salts, ammonium betaines, thioureas, phase-transfer catalysts and Brønsted acids have been successfully developed for this transformation.[6] As newly developed thiourea organocatalysts, the catalytic performance of **1a–1h** was first investigated in the catalytic aza-Henry reaction.

Initially, **1a–1h** were screened in the model reaction between aldimine (**2a**) and nitromethane (**3a**), which wass carried out in dichloromethane at −20 °C in the presence of 10 mol% of the catalyst. From Table 1, it can be seen that the organocatalysts derived from quinine are more active than the ones derived from cinchonine in this reaction (Table 1, entries 1, 2, 4 *vs.* 6, 7, 8). Compound **1e** derived from cinchonine and proline, which does not have an intact thiourea moiety, showed the lowest activity, suggesting the possibility of H-bonding as a mechanism of activation. Among **1a–1h**, **1h** derived from quinine and phenylalanine was selected for further optimization (entry 8).

The solvent always plays an important role in various catalytic processes. Different solvents were tested in the model reaction of benzaldehyde with nitromethane and the typical results are shown in Table 1 (entries 8–13). Using the non-polar solvent toluene, both the enantioselectivity and the chemical yield were inferior to those in dichloromethane (entry 9 *vs.* 8). With the polar protic solvents methanol, ethanol and isopropyl alcohol, good yields could be obtained, but the enantioselectivity was poor (entries 10, 11, 12). Surprisingly, when nitromethane was used directly as solvent, the yield was not improved, and the enantioselectivity decreased (entry 13 *vs.* 8). In the view of enantioselectivity, dichloromethane was the best choice for this reaction (entry 8).

The effect of temperature was also examined (entries 8, 14–16). When the reactions took place at room temperature and −10 °C, the yield increased at the expense of enantioselectivity (entries 14, 15 *vs.* 8). When the reaction was carried out at −40 °C, the

Table 1. Screening the parameters for the asymmetric aza-Henry reaction.[a]



2a **3a** **4a**

Entry	Ligand	Solvent	Additive	Temperature [°C]	Yield [%][b]	*ee* [%][c]
1	**1a**	CH_2Cl_2	–	−20	26	57
2	**1b**	CH_2Cl_2	–	−20	29	3
3	**1c**	CH_2Cl_2	–	−20	32	34
4	**1d**	CH_2Cl_2	–	−20	63	75
5	**1e**	CH_2Cl_2	–	−20	10	18
6	**1f**	CH_2Cl_2	–	−20	42	12
7	**1g**	CH_2Cl_2	–	−20	51	10
8	**1h**	CH_2Cl_2	–	−20	72	95
9	**1h**	toluene	–	−20	51	88
10	**1h**	MeOH	–	−20	75	30
11	**1h**	EtOH	–	−20	77	23
12	**1h**	*i*-PrOH	–	−20	80	46
13[d]	**1h**	CH_3NO_2	–	−20	73	89
14	**1h**	CH_2Cl_2	–	r.t.	96	88
15	**1h**	CH_2Cl_2	–	−10	87	91
16	**1h**	CH_2Cl_2	–	−40	41	94
17[e]	**1h**	CH_2Cl_2	DABCO	−20	81	65
18[e]	**1h**	CH_2Cl_2	DBU	−20	86	2
19[e]	**1h**	CH_2Cl_2	DMAP	−20	83	36
20[e]	**1h**	CH_2Cl_2	Et_3N	−20	77	62
21[e]	**1h**	CH_2Cl_2	NaOH	−20	86	38
22[e]	**1h**	CH_2Cl_2	Na_2CO_3	−20	83	90
23[e]	**1h**	CH_2Cl_2	pyridine	−20	75	95
24[e]	**1h**	CH_2Cl_2	Na_2HPO_4	−20	79	87
25[f]	**1h**	CH_2Cl_2	4 Å MS	−20	85	97

[a] All reactions were carried out with 0.125 mmol of **2a** and 1.25 mmol of nitromethane in 0.5 mL of solvent in the presence of 10 mol% catalyst for 12 h.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel AD-H).
[d] 0.5 mL of nitromethane were used as solvent.
[e] 0.5 equiv. of base were added.
[f] 25 mg of 4 Å molecular sieve were used.

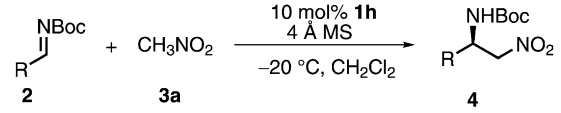
yield decreased obviously (entry 16 *vs* 8). Thus, −20 °C was selected as the optimized temperature.

Basic additives can deprotonate the nucleophiles in the Henry reaction, and this may affect the yield of the reaction. Therefore, several different basic additives were investigated in this reaction (Table 1, entries17–25). From Table 1 we can see that all the bases gave good yields but the *ee* values were different. 4 Å molecular sieve was reported to act as an effective proton scavenger of the protonic acid produced in some reactions, and to promote the reaction system.[7] In accord with our expectations, 4 Å molecular sieve was able to improve both the yield and the *ee* value (Table 1, entry 25) in this catalytic system.

With the optimized condition in hand, we then examined the scope and limitations of enantioselective aza-Henry reaction with various *N*-Boc-imines. A variety of imines reacted smoothly with nitromethane to afford the corresponding products (**4a–m**) in good yields (81–90%, Table 2). It appears that the position and the electronic property of the substituent on the aromatic rings have a very limited effect on the enantioselectivities. More than 96% *ee* values were obtained for the majority of these substrates, except for the 2-Cl-benzaldimine derivatives (92% *ee*, entry 4). Surprisingly, the aliphatic *N*-Boc-imine **2m**, which is generally difficult in aza-Henry reaction, gave the product with excellent enantioselectivity (98% *ee*) and good yield (81%) catalyzed by **1h**.

Highly diastereo- and enantioselective aza-Henry reactions that use nitroethane to form two stereocenters simultaneously still remain challenging and less explored compared to the reactions of nitromethane.[8] The good results obtained with nitromethane above prompted us to further evaluate the ligand **1h** in the aza-Henry reaction with nitroethane. The pre-

Table 2. Enantioselective aza-Henry reaction catalyzed by **1h**.[a]

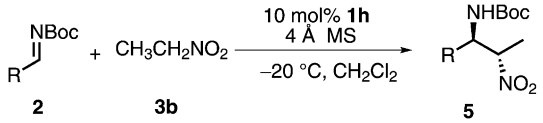


2 3a 4

Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph (**2a**)	85	97
2	4-Cl-C_6H_4 (**2b**)	86	97
3	3-Cl-C_6H_4 (**2c**)	82	98
4	2-Cl-C_6H_4 (**2d**)	87	92
5	4-Br-C_6H_4 (**2e**)	83	99
6	3-Br-C_6H_4 (**2f**)	84	98
7	2-Br-C_6H_4 (**2g**)	88	99
8	4-F-C_6H_4 (**2h**)	88	96
9	4-CF_3-C_6H_4 (**2i**)	85	99
10	4-MeO-C_6H_4 (**2j**)	89	99
11	2-MeO-C_6H_4 (**2k**)	90	96
12	1-naphthyl (**2l**)	85	96
13	cyclohexyl (**2m**)	81	98

[a] All reactions were carried out with 0.125 mmol of imines **2** and 1.25 mmol of nitromethane in 0.5 mL of dichloromethane in the presence of 10 mol% catalyst for 12 h at −20 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis using Chiralcel AD-H.

Table 3. Diastereo- and enantioselective aza-Henry reaction catalyzed by **1h**.[a]



2 3b 5

Entry	R	*dr*[b] [*anti:syn*]	Yield [%][c]	*ee* [%][d]
1	Ph (**2a**)	9:1	83	91
2	4-Cl-C_6H_4 (**2b**)	16:1	81	94
3	3-Cl-C_6H_4 (**2c**)	11:1	77	90
4	2-Cl-C_6H_4 (**2d**)	4:1	82	97
5	4-Br-C_6H_4 (**2e**)	6:1	83	89
6	3-Br-C_6H_4 (**2f**)	10:1	80	95
7	2-Br-C_6H_4 (**2g**)	3:1	79	96
8	4-F-C_6H_4 (**2h**)	17:1	81	90
9	1-naphthyl (**2j**)	8:1	85	85
10	4-Me-C_6H_4 (**2l**)	10:1	85	99

[a] All reactions were carried out with 0.125 mmol of imines **2** and 1.25 mmol of nitroethane in 0.5 mL of dichloromethane in the presence of 10 mol% catalyst for 12 h,at −20 °C.
[b] Assigned by HPLC data in combination with ^{1}H NMR data and comparison with literature reports.
[c] Isolated yield of the mixture.
[d] The *ee*s were determined by chiral HPLC analysis using Chiralcel AD-H, and here we report the *ee* value of *anti* configurations.

liminary results are summarized in Table 3. Under the mild conditions, all imines tested, bearing electron-rich, or electron-deficient groups, gave the products in good yields (77–85%) with high enantioselectivities (up to 99% *ee*) and diastereoselectivities (up to 17:1).

The experiment results give hints that the rational combination of the *Cinchona* alkaloid with the amino alcohol moiety indeed produces a perfect synergistic effect of stereocontrol. Mild conditions, easy availability of the catalysts and high steroselectivities make this new catalytic system attractive, providing a new practical access to a wide range of chiral β-nitro amines, which can be easily further transferred to vicinal diamines or α-amino carbonyl compounds as the intermediates for many biologically active compounds.[9]

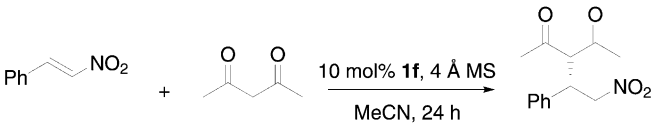
Michael Addition of Acetylacetone to Nitroolefins

The asymmetric Michael addition reactions of different carbon-centered nucleophiles to electron-deficient nitroolefins represent a direct and most appealing approach to synthetically valuable chiral nitroalkanes, in which the nitro functionality can be easily transformed into a nitrile oxide, ketone, amine, or carboxylic acid, and so on, providing a wide range of synthetically interesting compounds. Thus the development of chiral catalysts for this process has attracted many research groups. In 2003, Takemoto[10] developed a landmark chiral bifunctional organocatalyst for Michael additions of 1,3-dicarbonyl compounds to nitroalkenes, which involves an electron-withdrawing aryl substituent and a chiral tertiary amine group in a thiourea. Following this strategy, several thiourea-bifunctional organocatalysts were developed, and what's essential to their success is the ability to activate reactants through hydrogen bond interactions producing a well-defined orientation for the transition state of the process.[11]

To further extend the application of our new organocatalyst, **1a–1h** were screened in asymmetric Michael addition of acetylacetone to nitroolefins (Table 4, entries 1–8). Other parameters, such as solvent (Table 4, entries 6, 9–13), temperature (Table 4, entries 11, 14, 15) were also examined. From Table 4 we can see that **1f** derived from quinine and D-valine proved to be a good organocatalyst for this transformation. Under the optimized conditions, using 10% **1f** as catalyst, 4 Å MS as additive, acetonitrile as solvent at −40 °C, a good yield and high enantioselectivity could be obtained (Table 4, entry 15).

Table 5 shows the generality and scope of this catalyst system. Indeed, all tested nitroalkanes have

Table 4. Asymmetric Michael addition of acetylacetone and α-nitrostyrene **6a** under different conditions.[a]



6a **7** **8a**

Entry	Catalyst	Solvent	Temperature [°C]	Yield [%][b]	*ee* [%][c]
1	**1a**	CH_2Cl_2	−20	90	36
2	**1b**	CH_2Cl_2	−20	83	24
3	**1c**	CH_2Cl_2	−20	75	30
4	**1d**	CH_2Cl_2	−20	76	32
5	**1e**	CH_2Cl_2	−20	30	8
6	**1f**	CH_2Cl_2	−20	95	37
7	**1g**	CH_2Cl_2	−20	85	3
8	**1h**	CH_2Cl_2	−20	88	25
9	**1f**	THF	−20	68	29
10	**1f**	$CHCl_3$	−20	95	56
11	**1f**	MeCN	−20	92	81
12	**1f**	Et_2O	−20	93	41
13	**1f**	DMF	−20	30	17
14	**1f**	MeCN	−30	89	85
15	**1f**	MeCN	−40	87	90

[a] All reactions were performed on a 0.1-mmol scale with 10 mol% of catalyst at a 0.1 M concentration using 1 equiv. of α-nitrostyrene **6a** and 2 equiv. of acetylacetone for 24 h.
[b] Isolated yield.
[c] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel AD-H column.

Table 5. Asymmetric Michael addition of acetylacetone to nitroolefins catalyzed by organocatalyst **1f**.[a]

6 **7** **8**

Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph (**6a**)	87	90
2	4-Me-C_6H_4 (**6b**)	89	90
3	4-MeO-C_6H_4 (**6c**)	81	91
4	4-NO_2-C_6H_4 (**6d**)	89	90
5	4-CF_3-C_6H_4 (**6e**)	92	97
6	4-Br-C_6H_4 (**6f**)	82	95
7	4-Cl-C_6H_4 (**6g**)	90	88
8	2-Cl-C_6H_4 (**6h**)	95	90
9	4-F-C_6H_4 (**6i**)	89	94
10	3-Cl-C_6H_4 (**6j**)	85	90
11	1-naphthyl (**6k**)	93	91

[a] All reactions were performed on a 0.1-mmol scale with 10 mol% of catalyst at a 0.1 M concentration using 1 equiv. of **6** and 2 equiv. of acetylacetone in 24 h.
[b] Isolated yields.
[c] Enantiomeric excess (*ee*) was determined by chiral HPLC analysis (Chiralcel AD-H).

proven to be excellent substrates with respect to enantioselectivity and reactivity. The desired adducts were obtained in good yields (up to 93%) and synthetically useful levels of enantioselectivity (up to 97% *ee*), with substrates bearing both electron-donating (Table 5, entries 2 and 3) and electron-withdrawing substituents (Table 5, entries 4–10). It is also worth mentioning that **6f**, with a trifluoromethyl group on the phenyl ring, gave the best result with 92% yield and 97% *ee* (Table 5, entry 5). The substrate **6k** with the bulky naphthyl moiety (Table 5, entry 11) also gave the product in 93% yield and 91% *ee*. Here, the conjugate additions with β-alkyl-substituted nitroolefins were not investigated.

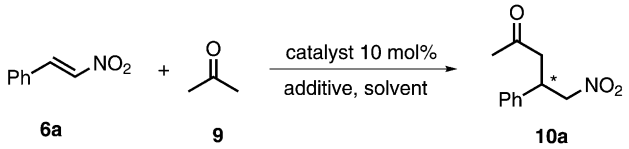
Michael Addition of Acetone to Nitroolefins

Since the organocatalytic asymmetric Michael addition of ketones to *trans*-β-nitrostyrene was pioneered by Barbas[12] and List[13] independently, great effort has been devoted to the development of more enantioselective and efficient catalytic systems for this synthetically useful transformation. However, acetone is still one of the most problematic substrates for the nitro-Michael addition due to its inactivity and smaller steric hindrance, which leads to difficulty to obtain good stereocontrol.[14] During the submission of this work, Kokotos developed a nice catalytic system using an amine-thiourea based on (1*R*,2*R*)-1,2-diphenylethylenediamine and (*S*)-di-*tert*-butyl aspartate for this transformation, and they also attributte the excellent results to a synergistic effect of enamine activation and the hydrogen bonding interaction.[15]

The organocatalysts **1a–1h** derived from *Cinchona* alkaloids and amino acids were examined in the model reaction between β-nitrostyrene (**6a**) and acetone (Table 6, entries 1–8). Different reaction conditions were screened, including solvents (entries 3, 9–12), additives (entries 10, 13–19) and temperatures (entries 10, 19–21). From Table 6, we can see that **1c** was the optimized catalyst and the non-polar solvent toluene was the best choice for this reaction. Both base additives and acid additives were investigated, however, 4 Å MS gave good yield and excellent enantioselectivity. In a word, the optimized conditions for the β-nitrostyrene (**6a**) and acetone are as following: using 10% **1c** as catalyst, 4 Å MS as additive, toluene as solvent at 5 °C.

Table 7 shows the generality of this methodology. As shown in Table 7, all the nitroalkenes reacted with acetone smoothly to afford the corresponding γ-nitro carbonyl compounds in good yields. It is encouraging

Table 6. Screening of conditions for the asymmetric Michael addition of acetone and α-nitrostyrene **6a**.[a]



6a **9** **10a**

Entry	Catalyst	Solvent	Additive	Temperature [°C]	Yield [%][b]	*ee* [%][c]
1	**1a**	MeCN	–	r.t.	21	40
2	**1b**	MeCN	–	r.t.	trace	nd[d]
3	**1c**	MeCN	–	r.t.	45	43
4	**1d**	MeCN	–	r.t.	55	7
5	**1e**	MeCN	–	r.t.	20	29
6	**1f**	MeCN	–	r.t.	trace	nd[d]
7	**1g**	MeCN	–	r.t.	trace	nd[d]
8	**1h**	MeCN	–	r.t.	24	26
9	**1c**	EtOH	–	r.t.	88	36
10	**1c**	toluene	–	r.t.	70	67
11	**1c**	acetone	–	r.t.	91	54
12	**1c**	Et_2O	–	r.t.	54	66
13[e]	**1c**	toluene	TFA	r.t.	57	99
14[e]	**1c**	toluene	AcOH	r.t.	71	46
15[e]	**1c**	toluene	PhOH	r.t.	72	43
16[e]	**1c**	toluene	DIPEA	r.t.	73	45
17[e]	**1c**	toluene	DMAP	r.t.	74	47
18[e]	**1c**	toluene	benzylamine	r.t.	97	8
19[e]	**1c**	toluene	4 Å MS	r.t.	79	85
20[e]	**1c**	toluene	4 Å MS	0	59	99
21[f]	**1c**	toluene	4 Å MS	5	83	98

[a] All reactions were carried out using α-nitroolefin **6** (0.1 mmol), acetone (1 mmol, 10 equiv.) and 0.01 mmol organocatalyst for 4 d.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by chiral HPLC analysis.
[d] nd = not determined.
[e] 0.1 equiv. additive was added. For 4 Å molecular sieve, 25 mg were used.
[f] The reaction lasts 8 d.

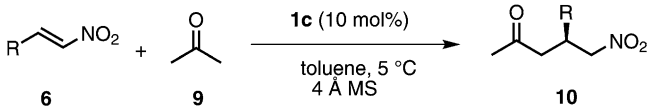
that excellent enantioselectivities (more than 98% *ee*) were observed for various substrates bearing either electron-donating or electron-withdrawing substituents in the *para*, *meta*, or *ortho* position of the aromatic ring, regardless of the nature and the position of the substituted group on the aromatic ring. Moreover, the heteroaromatic furyl substrate **6p** also gave good yield and excellent enantioselectivity (entry 13).

To understand the high enantioselectivities observed in the **1c**-promoted Michael addition of acetone to nitroolefins, the absolute configuration of the organocatalyst **1c** and the Michael adduct **10h** were identified by their crystal structures (Figure 2).[16] As with other bifunctional organocatalysts, we think that the thiourea functionality interacts through hydrogen bondings with the nitro group of the nitroolefin, meanwhile the hydroxy group from the amino alcohol moiety and the nitro group may form another hydrogen bond, which enhances the electrophilicity of the nitroolefins. On the other hand, the tertiary amine of the azabicyclo moiety in the quinine, acting as a base, deprotonates an acidic proton of acetone, and generates a ternary complex. In a word, the multiple hydrogen bonding interactions and base-acid interaction between the catalyst and the substrates may be synergistically responsible for the excellent enantioselectivities. Nevertheless, the real catalytic mechanism still needs further investigation.

Conclusions

In conclusion, we have developed a new series of modular bifunctional chiral organocatalysts for the highly enantioselective aza-Henry reaction of nitroalkanes to imines, the Michael addition of acetylacetone to nitroolefins and the Michael addition of acetone to nitroolefins. The important building blocks β-nitro amines and γ-nitro carbonyl compounds could be obtained in good yields (up to 95%) with excellent enantioselectivities (up to 99% *ee*) and diastereoselectivities (up to 17:1).

Table 7. Asymmetric Michael addition of acetone to nitroolefins catalyzed by organocatalyst **1c**.[a]



6 9 10

Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph (**6a**)	83	98
2	4-CH_3-C_6H_4 (**6b**)	91	99
3	4-MeO-C_6H_4 (**6c**)	79	99
4	4- NO_2-C_6H_4 (**6d**)	77	99
5	4-CF_3-C_6H_4 (**6e**)	75	99
6	4-Br-C_6H_4 (**6f**)	71	99
7	4-Cl-C_6H_4 (**6g**)	75	99
8	2-Cl-C_6H_4 (**6h**)	76	99
9	4-F-C_6H_4 (**6l**)	73	99
10	2-NO_2-C_6H_4 (**6m**)	92	99
11	3-NO_2-C_6H_4 (**6n**)	91	99
12	4-CN-C_6H_4 (**6o**)	82	99
13	2-furyl (**6p**)	80	99

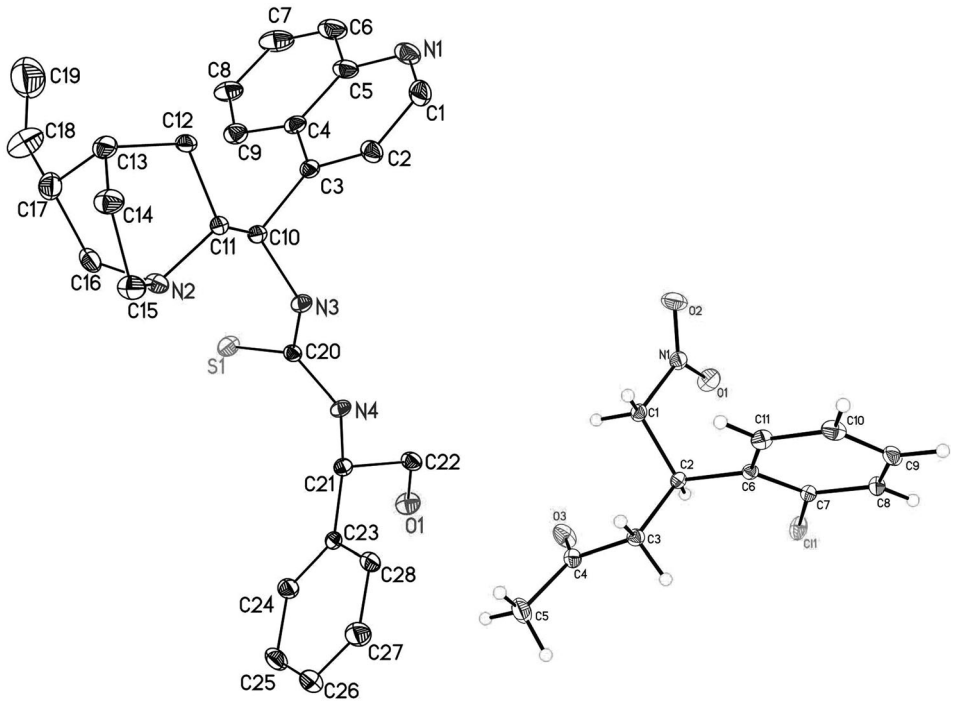
[a] All reactions were carried out using α-nitroolefin **6** (0.1 mmol), acetone (1 mmol, 10 equiv.) and **1c** (0.01 mmol) in the presence of 25 mg 4 Å MS in toluene (1 mL) at 5 °C in 8 d.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

Due to the synergistic effect through combining the *Cinchona* alkaloid with amino alcohol moieties, some usually difficult substrates, especially acetone as substrate in Michael addition achieve a perfect stereocontrol. Considering the easy availability of the catalysts, mild conditions, without other additives except molecular sieves and high enantioselectivities, these methodologies demonstrate the versatility and practicability of these new organocatalysts. Further investigation into the catalytic mechanism and applications of these transformations to bioactive molecular synthesis is ongoing in our laboratory.

Experimental Section

General Remarks

All reactions were carried out under an argon atmosphere in oven-dried glassware with magnetic stirring. Starting materials and reagents were purchased from commercial suppliers and used without further purification. Solvents were distilled before use: THF and diethyl ether from sodium metal/benzophenone, CH_2Cl_2 from calcium hydride. ^{1}H NMR spectra were recorded on 400 MHz spectrometers. The samples were dissolved in $CDCl_3$, MeOD or DMSO and data are reported in ppm. Splitting patterns were reported as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded using a 100 MHz instrument with samples dissolved in DMSO,

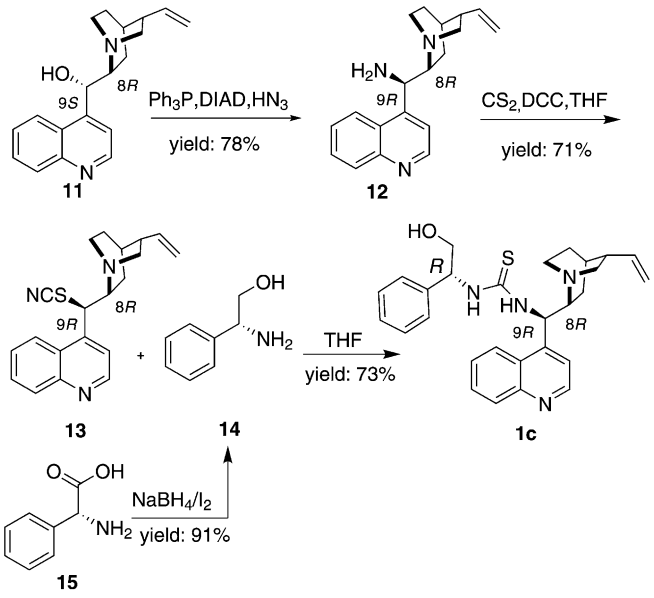


a) catalyst **1c**. b) **10h**.

Figure 2. X-ray crystal structures of **1c** and **10h**.

MeOD or $CDCl_3$ and data are reported in ppm. Mass spectra were recorded using ESI or EI techniques. HPLC analyses were carried out on a chromatograph equipped with a UV detector using different chiral colums, as indicated for the description of each product (see below).

Procedure for the Synthesis of Catalysts 1a–1h with 1c as Example



Diisopropyl azodicarboxylate (DIAD, 2.5 mL, 12.5 mmol) was added to a solution of the cinchonine (2.94 g, 10 mmol) and triphenylphosphine (3.28 g, 12.5 mmol) in absolute THF (30 mL) at 0 °C all at once. After 5 min, a solution of HN_3 (17 mL, 12.5 mmol) in dry $CHCl_3$ was added dropwise at 0 °C. The mixture was warmed to room temperature. After being stirred overnight, the solution was heated at 60 °C for 24 h. Then, triphenylphosphine (3.28 g, 12.5 mmol) was added, and the heating was maintained until the gas evolution had ceased. The solution was cooled to room temperature, and water (10 mL) was added. After stirring for 24 h, the solvents were removed, and the residue was dissolved in DCM and 2 M HCl (1:1, 70 mL). The aqueous phase was extracted with DCM (30 mL × 3). Then, the aqueous phase was made alkaline with a saturated aqueous solution of Na_2CO_3 and extracted with DCM. Concentration of the dried extracts afforded a residue, which was purified by column chromatography to afford 9-amino-9-deoxyepicinchonine **12**; yield: 2.23 g (78%).

To a solution of **12** (400 mg, 1.36 mmol) in dry THF (1.36 mL) at −10 °C were added CS_2 (0.5 mL, 8.18 mmol) and DCC (280.6 mg, 1.36 mmol). The reaction mixture was warmed slowly to room temperature over a period of 3 h and then stirred at room temperature overnight. The precipitate was removed by filtration, and the solvent was subsequently removed under vacuum. The residue was taken up in diethyl ether. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography to afford the product 9-deoxyepiquinidine isothiocyanate **13**; yield: 352 mg (71%).

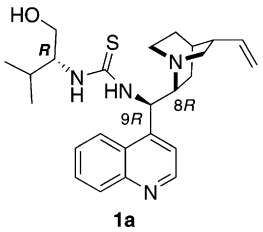
To a solution of $NaBH_4$ (662 mg, 17.5 mmol) and D-phenylglycine **15** (1.06 g, 7 mmol) in dry THF (30 mL) at 0 °C were added a solution of I_2 (2.13 g , 8.4 mmol in 10 mL THF) slowly. Then, the solution was heated at 64 °C for 18 h. The solution was cooled to room temperature, and MeOH was added drop by drop until the solution getting clear. After stirring for 30 min, the solvent was removed under reduced pressure and the residue was added 20% KOH (20 mL). After stirring for 4 h, the aqueous phase was extracted with DCM (30 mL × 4). The solvent was removed under reduced pressure, and the residue was the intermediate **14**; yield: 900 mg (91%).

A solution of the **14** in THF (0.6 M) was added to a stirred solution of the isothiocyanate **13** in THF (0.6 M) at room temperature. After 48 h, the solvent was removed under reduced pressure. The residue was purified by column chromatography to afford the desired product **1c**; yield: 73%.

The others catalysts were synthesized according to similar procedures.

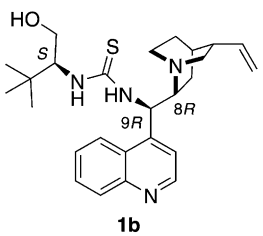
^{1}H and ^{13}C NMR and HR-Mass Spectra Data for the Organocatalysts 1a–1h

Calalyst 1a:



White solid; yield: 76%; mp 127–129 °C; [α]: +19.00 (*c* 0.25, CH_3OH); IR (KBr): ν = 3261, 3063, 2955, 2937, 2872, 1590, 1540, 1510, 1466, 1337, 1312, 1265, 1242, 1068, 991, 918, 849, 762, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.89 (d, 1 H, J = 4.0 Hz), 8.39 (br s, 1 H),8.18 (d, 1 H, J = 8.0 Hz), 7.78 (t, 1 H, J = 7.4 Hz), 7.67(t, 1 H, J = 7.6 Hz), 7.48(s, 2 H), 5.87 (t, 1 H, J = 3.2 Hz), 5.19 (d, 2 H, J = 9.6 Hz), 4.33 (br s, 1 H), 3.77 (t, 1 H, J = 8.6 Hz), 3.58 (s, 1 H), 3.51 (d, 1 H, J = 6.8 Hz), 3.19 (br s, 1 H), 3.03 (m, 2 H), 2.35 (m, 6 H),1.67–1.50 (m, 3 H), 1.25–1.19 (m, 1 H), 0.98–0.92 (m, 1 H), 0.68–0.49 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 182.8, 150.2, 148.7, 139.7, 130.8, 129.9, 127.5, 115.3, 77.4, 76.9, 76.9, 76.7, 48.8, 47.1, 39.0, 27.3, 26.2, 25.0, 24.8, 19.2, 19.0, 18.3, 15.3; HR-MS (ESI$^+$; free base): m/z = 439.2529, calcd. for $C_{25}H_{34}N_4OS$ $(M+H)^+$: 439.2532.

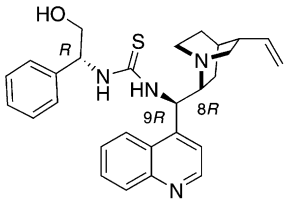
Calalyst 1b:



White solid; yield: 81%; mp 188–190 °C; [α]: +9.12 (*c* 0.25, CH_3OH); IR (KBr): ν = 3244, 3060, 2961, 2874, 1639, 1545, 1472, 1362, 1339, 1267, 1240, 1086, 1051, 1022, 999,

928, 851, 770, 731 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ = 8.85 (d, 1H), 8.49 (d, 1H), 8.01 (d, 1H), 7.73 (d, 1H), 7.60 (dd, 2H), 7.45 (dd, 1H), 5.89–5.98 (m, 1H), 5.11–5.20 (m, 2H), 4.59 (s, 1H), 4.00 (d, 1H), 3.40 (m, 6H), 3.07 (s, 1 H), 2.93(s, 4H), 2.27 (s, 1H), 1.46–1.52 (s, 3H), 1.12–0.7 (s, 9H); ^{13}C NMR (100 MHz, DMSO): δ = 182.6, 150.1, 148.6, 147.8, 140.6, 129.5, 128.8, 127.1, 126.0, 124.5, 124.3, 119.6, 114.7, 62.2, 60.6, 60.2, 48.5, 46.6, 34.3, 33.4, 27.1, 27.0, 25.8, 24.8, 24.6; HR-MS (ESI$^+$; free base): m/z = 453.2691, calcd. for $C_{26}H_{36}N_4OS$ $(M+H)^+$: 453.2688.

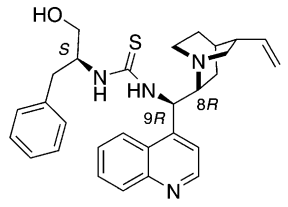
Calalyst 1c:



1c

White solid; yield: 73%; mp 154–156 °C; [α]: +10.92 (*c* 0.25, CH_3OH); IR (KBr): ν = 3252, 3059, 3032, 2932, 2870, 1589, 1539, 1510, 1495, 1454, 1352, 1335, 1063, 1028, 918, 851, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.77 (s, 1H), 8.25 (br s, 1H), 8.12 (d, 1H, J = 8.4 Hz), 7.74 (t, 2H, J = 7.2 Hz), 7.57 (s, 2H), 7.43–7.16 (m, 5H), 5.87–5.85 (m, 1H), 5.30 (s, 1H), 5.12–5.17 (m, 2H), 3.80–3.89 (m, 3H), 3.51 (dd, 1H, J = 6.8 Hz), 2.96 (m, 4H), 2.32 (dd, 2H, J = 7.2 Hz), 2.17 (br s, 1H), 1.64–1.47(m, 3H), 1.21 (dd, 1H, J = 6.8 Hz), 0.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 181.3, 145.0, 148.3, 139.6, 138.4, 130.2, 129.3, 128.0, 126.7, 123.8, 123.7, 115.3, 66.2, 66.7, 53.5, 48.8, 47.1, 39.0, 27.3, 26.1, 25.6, 25.0, 15.3, 12.0; HR-MS (ESI$^+$; free base) m/z = 473.2381, calcd. for $C_{28}H_{32}N_4OS$ $(M+H)^+$: 473.2370.

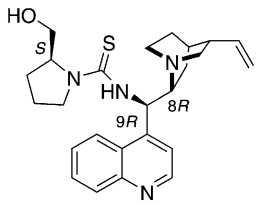
Calalyst 1d:



1d

White solid; yield: 81%; mp 115–118 °C; [α]: +8.20 (*c* 0.25, CH_3OH); IR (KBr): ν = 3250, 3059, 3028, 2935, 2878, 1531, 1512, 1495, 1454, 1387, 1335, 1265, 1086, 1032, 991, 920, 851, 748, 702 cm^{-1}; ^1H NMR ($CDCl_3$,400 MHz): δ = 8.88 (d, 1H, J = 4.4 Hz), 8.45 (d, 1H, J = 4.8 Hz), 8.14 (dd, 1H), 7.77 (dd, 1H), 7.66–7.54 (m, 2H), 7.32 (br s, 1H), 7.25–7.15 (m, 5H), 5.90–5.81 (m, 1H), 5.29–5.23 (m, 2H), 4.58 (br s, 1H), 3.65 (m, 1H), 3.54 (m, 1H), 3.42 (m, 1H), 3.21 (m, 1H), 3.12–2.87 (m, 6H), 2.78 (m, 1H), 2.43 (m, 1H), 1.73–1.62 (m, 3H), 1.29 (m, 1H), 1.05–1.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 182.4, 150.5, 150.3, 148.6, 139.7, 139.4, 138.5, 137.7, 130.3, 129.6, 129.3, 128.9, 128.4, 127.2, 126. 9, 126.4, 124.1, 123.9, 120.0, 116.1, 115.6, 62.6, 61.2, 57.3, 48.9, 46.9, 38.1, 37.1, 27.0, 25.1, 24.6; HR-MS (ESI$^+$; free base): m/z = 487.2529, calcd. for $C_{29}H_{34}N_4OS$ $(M+H)^+$: 487.2532.

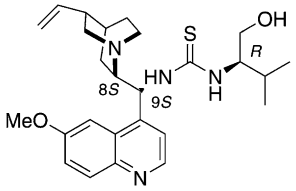
Calalyst 1e:



1e

White solid; yield: 57%; mp 134–136 °C; [α]: +4.72 (*c* 0.25, CH_3OH); IR (KBr): ν = 3249, 3074, 2932, 2872, 1508, 1456, 1402, 1352, 1076, 1047, 914, 866, 851, 754, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.84 (d, 1H), 8.85 (dd, 1H), 8.09 (d, 1H), 7.70 (s, 1H), 7.60 (dd, 1H), 7.44 (s, 1H), 5.88–5.93 (dd, 2H), 5.22 (dd, 2H), 4.71 (dd, 1H), 3.63–3.65 (m, 4H), 3.02 (s, 6 H), 2.35 (s, 1H), 2.03 (s, 3H), 1.78 (dd, 1H), 1.21–1.69 (m, 5H), 0.92 (s, 1H); ^{13}C NMR (100 MHz, MeOD): δ = 150.9, 148.8, 141.3, 130.9, 129.6, 129.2, 127.8, 126.6, 115.5, 61.8, 61.3, 40.2, 28.8, 27.0, 26.8, 26.1, 24.4; HR-MS (ES; free base): m/z = 437.2380, calcd. for $C_{25}H_{32}N_4OS$ $(M+H)^+$: 437.2370.

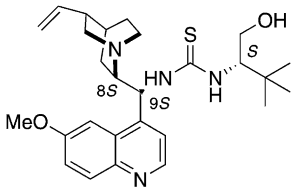
Calalyst 1f:



1f

White solid; yield: 76%; mp 136–138 °C; [α]: −6.40 (*c* 0.25, CH_3OH); IR (KBr): ν = 3261, 3070, 2957, 2935, 2870, 1622, 1531, 1510, 1474, 1362, 1263, 1242, 1229, 1173, 1186, 1080, 1030, 987, 918, 852, 736; ^1H NMR (DMSO, 400 MHz): δ = 8.47 (d, 1H), 7.92 (d,1H), 7.67 (d, 2H), 7.18–7.21 (m, 2H), 5.56–5.58 (m, 2H), 4.67–4.77 (dd, 2H), 4.45 (s, 1H), 3.70 (s, 3H), 2.98–3.26 (d, 9H), 2.46 (s, 1H), 2.04 (s, 1H), 1.60 (s, 1H), 1.34 (s, 3H), 0.96 (s, 1H), 0.49–0.60 (m, 5H); ^{13}C NMR (100 MHz, DMSO): δ = 182.1, 156.9, 147.5, 144.1, 141.6, 131.1, 127.9, 121.2, 114.4, 103.1, 60.5, 59.8, 55.6, 55.6, 55.0, 40.9, 28.1, 27.0, 25.3, 19.2, 18.2; HR-MS (ESI$^+$; free base): m/z = 469.2642, calcd. for $C_{26}H_{36}N_4OS$ $(M+H)^+$: 469.2632.

Calalyst 1g:

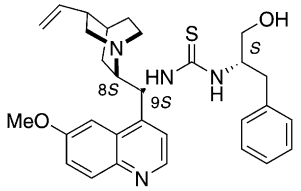


1g

White solid; yield: 68%; mp 153–156 °C; [α]: −12.88 (*c* 0.25, CH_3OH); IR (KBr): ν = 3256, 3070, 2951, 2868, 1622,

1540, 1508, 1475, 1366, 1263, 1240, 1229, 1084, 1030, 918, 854, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.79$ (d, 1H), 8.06 (dd, 1H), 7.70 (d, 2H), 7.43 (s, 2H), 6.46 (dd, 1H), 6.09 (dd, 1H), 5.71 (dd, 1H), 5.04 (d, 2H), 4.40 (dd, 1H), 3.87–4.01 (m, 4H), 3.24–3.50 (m, 4H), 2.82 (m, 3H), 2.37 (s, 1H), 1.46–1.73 (m, 4H), 0.99–0.97 (m, 9H), 0.80–0.96 (m, 4H), 0.38–0.36 (m, 5H); ^{13}C NMR (100 MHz, DMSO): $\delta = 156.9$, 156.7, 149.2, 147.5, 144.0, 143.9, 142.5, 141.9, 131.1, 127.0, 121.2, 120.9, 119.1, 114.2, 114.1, 102.9, 102.4, 70.8, 60.6, 55.8, 55.5, 55.0, 41.7, 27.4, 26.4, 24.0; HR-MS (ESI^+; free base): $m/z = 483.2782$, calcd. for $C_{27}H_{38}N_4O_2S$ $(M+H)^+$: 483.2788.

Calalyst 1h:



1h

White solid; yield: 77%; mp 133–136 °C; [α]: −10.72 (*c* 0.25, CH_3OH); IR (KBr): $\nu = 3252$, 3061, 3028, 2932, 2864, 1622, 1531, 1510, 1474, 1454, 1346, 1263, 1229, 918, 852, 737, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz):$\delta = 8.70$ (d, $J =$ 4.4 Hz, 1H), 8.01 (d, $J = 9.6$ Hz, 1H),7.86 (s, 1H),7.67 (s, 1H),7.42 (m,1H), 7.40 (q, $J = 4.4$ Hz, 1H), 7.20 (m, 3H), 7.09 (s, 2H), 5.68 (br s, 1H), 4.98 (m, 2H), 3.99 (s, 3H), 3. 67–3.65 (m, 2H), 3.54 (s, 2H), 3.33 (s, 2H), 3.20 (m, 2H), 2.76 (m, 3H), 2.65 (s, 1H), 2.35 (s, 1H), 1.70 (s, 3H), 1.41(s, 1H), 0.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 182.0$, 158.1, 147.5, 144.7, 140.2, 131.6, 129.1, 128.5, 126.6, 126.8, 122.3, 115.3, 102.2, 77.4, 77.0, 76.7, 57.7, 56.0, 55.1, 41.4, 38.8, 37.1, 27.1, 25.6, 15.3; HR-MS (ESI^+; free base): $m/z =$ 517.2640, calcd. for $C_{30}H_{36}N_4O_2S$ $(M+H)^+$: 517.2632.

General Procedure for Aza-Henry Reaction of Nitroalkanes to *N*-Boc-imines

A mixture of *N*-Boc-imine **2** (0.125 mmol), **1h** (0.0125 mmol), and 25 mg of 4 Å MS in 0.5 mL of dichloromethane was cooled to −20 °C and stirred. Then the nitroalkane (1.25 mmol) was added. The reaction was monitored by thin layer chromatography. After evaporation of the solvent, the residue was purified by flash chromatography on a silica gel column (hexane/EtOAc = 10:1) to afford the product **4** or **5**. Enantiomeric excesses were determined by HPLC with a Chiralcel AD-H column.

General Procedure for Michael Addition Reactions of Acetylacetone to Nitroolefins

A mixture of α-nitroolefin **6** (0.1 mmol), **1f** (0.01 mmol) and 25 mg of 4 Å MS in 1 mL acetonitrile was cooled to −40 °C. Then acetylacetone (0.2 mmol) was added and the mixture stirred overnight. The reaction was monitored by thin layer chromatography. After evaporation of the solvent, the residue was purified by flash chromatography on a silica gel column (hexane/EtOAc = 3:1) to afford the product **8**. Enantiomeric excesses were determined by HPLC with a Chiralcel AD-H column.

General Procedure for Michael Addition Reactions of Acetone to Nitroolefins

A mixture of α-nitroolefin **6** (0.1 mmol), **1c** (0.01 mmol), acetone (1 mmol, 10 equiv.) and 25 mg of 4 Å MS in 0.5 mL toluene was stirred at 5 °C, the reaction was monitored by thin layer chromatography. After evaporation of the solvent, the residue was purified by flash chromatography on a silica gel column (hexane/EtOAc = 4:1) to afford the product **10**. Enantiomeric excesses were determined by HPLC with a Chiralcel AD-H column.

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[16] CCDC 862556 and CCDC 862557 contain the crystallographic data for organocatalyst **1c** and 5-nitro-4- (2-chlorophenyl) pentan-2-one **10h**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.