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A Chiral Functionalized Salt-Catalyzed Asymmetric Michael Addition of Ketones to Nitroolefins

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Abstract: The chiral functionalized salt catalysis, which differs from the known enzyme- and transition metal-based methods, has been successfully developed to carry out the Michael addition of ketones to nitroolefins. Chiral anion salt (type **I**), chiral cation salt (type **II**), or chiral anion-chiral cation salt (type **III**) could be expected to be remarkably effective catalysts and afford the corresponding chemically and optically pure Michael addition adducts. A primary amine group activating the ketone during salt catalysis was their obvious and common property. Based on preliminary experimental investigations and previous reports on primary amine catalysis, a reaction pathway *via* imine, enamine, iminium ion to imine was proposed.

Keywords: amino acids; diamines; Michael addition; nitroolefins; salt catalysis

Introduction

Salt catalysts, especially chiral functionalized salt catalysts (Figure 1, types **I**, **II** and **III**), have attracted growing attention recently, due to their tuneable features for various chemical tasks, their advantages in a convenient recovering and reusing process,[1–3] and their possibilities in relation to structural modification of either the cation or anion. In developing chiral anion amino acid salts (type **I**), bifunctional sodium (*S*)-aminophenylacetate has been developed for application in the asymmetric cyanosilylation of ketones in our previous studies.[3] As a counterpart, chiral positive ion quaternary ammonium salts and chiral oxazaborolidinium ion salts (type **II**) have largely emerged as remarkably potent, useful and versatile chiral catalysts for asymmetric processes,[2] whereas ammonium salt, $-NH_3^+$ or $=(NH_2)^+$, catalysis has appeared sporadically in catalytic asymmetric reactions. There is a logic in expecting catalysts (type **III**), whose cation and anion are both chiral, to effectively promote some asymmetric reactions. In this regard, Barbas III used an ammonium salt (Figure 2) to catalyze aldol reactions.[1e,f]

Since the initial pioneering works,[4,5] remarkable advances in the application of secondary amines, such as pyrrolidine- and imidazoline-type chiral organocatalysts, on the Michael addition of carbonyl compound to nitroalkenes have been reported,[6] in which

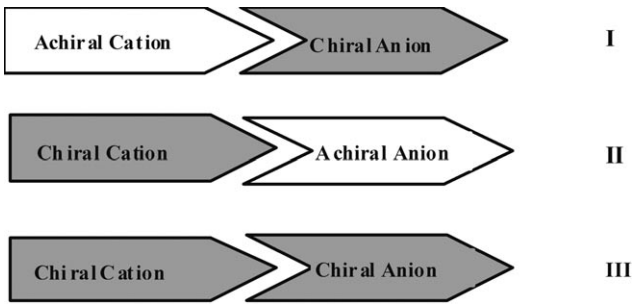


Figure 1. Combinations of chiral functional salts.

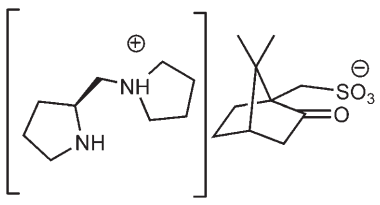


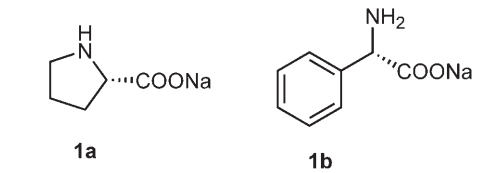
Figure 2. Barbas III's ammonium salt.

the asymmetric *enamine catalysis* of carbonyl transformations has been commonly accepted, and initially proceeded *via* iminium ion formation and almost always ultimately resulted in iminium ion formation.[7] By comparison, besides effective primary amine-thiourea catalysis,[8] little progress has been made *via enamine catalysis* in the development of chiral small-molecule primary amine catalysts, especially of the primary amine-salt catalyst system. Nevertheless, primary amine catalysis was effectively exploited using enzymes such as type I aldolases, decarboxylases and dehydratases, each of which contains catalytically active lysine residues.[9] Considering the particularities and potentials of the primary amine-salt catalysis, we now report on the primary amine salt-catalyzed asymmetric Michael addition of ketones to nitroolefins *via enamine catalysis*, which is initiated *via* imine formation and ultimately resulted in imine formation, and which also could deliver excellent reactivities and selectivities.

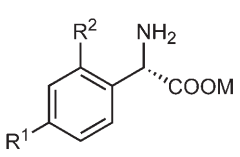
Results and Discussion

Achiral Cation-Chiral Anion Salt Catalysis

We firstly become interested in the possible use of chiral anion salt catalysis (type **I**) in the asymmetric Michael addition of ketones to nitroolefins. Catalysts **1a–b** and **1d–h** (Figure 3) were prepared by treating the amino acid with an equivalent of MOH (M = Li, Na and K) in methanol. The Michael addition of cyclohexanone to nitrostyrene, as a model reaction, was then explored to determine the optimal conditions, with the initial results being summarized in Table 1. As the data show, compared to pyrrolidine-type chiral amino acid salt **1a**, sodium (*S*)-aminophenylacaetate **1b** was prominent in providing the Michael addition product in 95% yield with a better enantioselectivities (61% *ee*) under the conditions of 20 mol% catalyst loading, and solvent-free at room temperature, which also preliminarily demonstrates the possible efficient use of a primary amine in salt catalytic systems (entries 1 and 2).[10]



1a **1b**



1c: R^1 = Cl, R^2 = H, M = H
1d: R^1 = Cl, R^2 = H, M = Li
1e: R^1 = Cl, R^2 = H, M = Na
1f: R^1 = Cl, R^2 = H, M = K
1g: R^1 = F, R^2 = H, M = K
1h: R^1 = H, R^2 = Cl, M = K

Figure 3. The evaluated chiral anion catalysts.

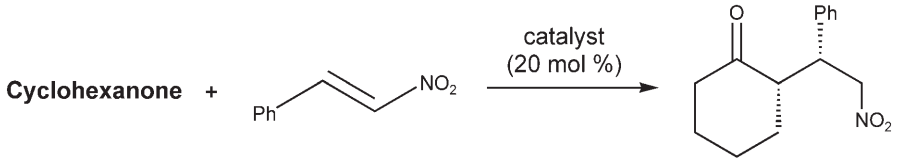
The substituent on the phenyl group, solvent, catalyst loading and the cation were all consecutively investigated. At 0 °C, catalyst **1b** only gave a trace of product under solvent-free conditions (entry 3). Although the chloro-substituent on the *para*-position of the phenyl group (**1e**) gave the same enantiomeric excess (61% *ee*) at room temperature (entry 6), the enantioselectivity could also be improved up to 72% *ee* without the loss of isolated yield and diastereoselectivity after 12 h at 0 °C (entry 7). At room temperature, a routine solvent screen established that *m*-xylene was the most effective in terms of the yields and selectivities (entry 8 *vs.* 10–14). With *m*-xylene, decreasing the temperature to 0 °C was favorable and increased the enantioselectivity to 79% *ee* (entry 9 *vs.* 8). Meanwhile, in the presence of lower (10 mol%) or higher (30 mol%) catalyst loadings, inferior asymmetric induction was recorded (entries 15 and 16). Replacing cation Na^+ with H^+, Li^+, or K^+ showed that the transition from metal to non-metal and decreasing effective cation size led to decreasing reactivity and enantioselectivity, with even amino acid **1c** having no reaction. The catalyst **1f** afforded good enantioselectivities up to 84% *ee* at 0 °C and 87% *ee* at −20 °C with acceptable diastereoselectivities (entries 17 and 18). The fluoro-substituent on the *para*-position or the chloro-substituent on the *ortho*-position of the phenyl group (**1g** or **1h**) gave lowered enantiomeric excesses (entries 19 and 20). Therefore, we found that treatment of nitrostyrene and cyclohexanone with catalyst **1f** (20 mol%) in *m*-xylene led to the most efficient enantioselective formation of product.

Under the optimal conditions, the substrate generality was examined, and the results are listed in Table 2. Various styrene-type nitroolefins worked well in this reaction to obtain good diastereoselectivities (up to 96:4 *syn*/*anti*) and enantioselectivities (up to 95% *ee*). For some of the substrates, temperature effects were also examined. Decreasing the temperature from 0 to −20 °C, with relatively lower reactivities, the selectivities were all improved. The reactions of cyclopentanone and acetone with nitrostyrene could also give adducts in moderate yields with good selectivities (entries 17 and 18).

Chiral Cation-Achiral Anion Salt Catalysis

Attempting to develop a chiral cation salt (type **II**) and based on Barbas III's ammonium salt (Figure 2), we considered the combination of a chiral amine and a protonated amine positive ion to activate ketones *via* enamine formation and simultaneously activate ni-

Table 1. Optimization studies.



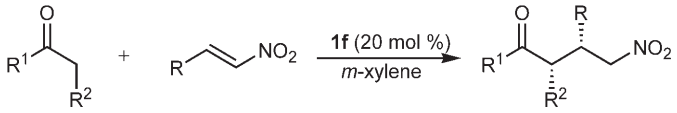
Entry[a]	Catalyst	Solvent[b]	Temperature [°C]	*t* [h]	Yield [%][c]	*dr* [*syn/anti*][d]	*ee* [%][e]
1	**1a**	neat	r.t.	4	96	96:4	18
2	**1b**	neat	r.t.	4	95	90:10	61
3	**1b**	neat	0	12	trace	–	–
4[f]	**1c**	*m*-xylene	0	12	n.r.	–	–
5	**1d**	*m*-xylene	0	12	11	69:31	8
6	**1e**	neat	r.t.	4	95	92:8	61
7	**1e**	neat	0	12	95	89:11	72
8	**1e**	*m*-xylene	r.t.	4	95	92:8	69
9	**1e**	*m*-xylene	0	12	93	93:7	79
10	**1e**	CH_2Cl_2	r.t.	4	92	83:17	61
11	**1e**	toluene	r.t.	4	92	84:16	65
12	**1e**	*o*-xylene	r.t.	4	93	89:11	67
13	**1e**	hexane	r.t.	4	94	85:15	68
14	**1e**	THF	r.t.	4	90	80:20	55
15[g]	**1e**	*m*-xylene	0	12	23	90:10	70
16[h]	**1e**	*m*-xylene	0	12	93	87:13	77
17	**1f**	*m*-xylene	0	12	98	76:24	84
18	**1f**	*m*-xylene	−20	36	80	82:18	87
19	**1g**	*m*-xylene	0	12	82	90:10	77
20	**1h**	*m*-xylene	0	12	91	92:8	73

[a] All reactions were carried out on a scale of 0.1 mmol nitrostyrene and 0.2 mL cyclohexanone.
[b] 0.2 mL solvent.
[c] Isolated yield.
[d] Determined by ^{1}H NMR spectroscopy.
[e] Determined by HPLC analysis.
[f] n.r. = no reaction.
[g] 10 mol% catalyst loading.
[h] 30 mol% catalyst loading.

troalkenes *via* a hydrogen bond of −CONH− and ion $-NH_n^+$ ($n=1$–3) interacting with the $-NO_2$ group. This approach was also partly motivated by recent successes in the application of similar diamine backbones as bifunctional catalysts in the asymmetric cyanosilylation of ketones and aldehydes.[11]

Salts **2, 3, 5** and **6** (Figure 4) were prepared *in situ* by treating diamine derivatives with an equivalent of 4-toluenesulfonic acid (see Experimental Section). The model reactions of cyclohexanone and nitrostyrene were carried out in neat mixtures with 15 mol% catalyst loading at room temperature for 10 h, and the results are summarized in Table 3. Secondary amine salts **2** and **3** derived respectively from (*R*,*R*)- and (*S*,*S*)-diamine gave the same configuration of products (see Supporting Information) and almost equal enantioselectivity, which revealed that the absolute configuration of the chiral diamine moiety had little effect on the asymmetric induction (entries 1 and 2). Based on the *R*,*R*-diamine moiety, systematic screening studies[12] established that (*S*)-2-amino-2-phenylacetic acid-derived primary amine salt **5** could most effectively promote the enantioselective addition (entry 6). For diamine derivative **4**, 4-toluenesulfonic acid additive (5 mol%) provided relatively inferior results, and 30 mol% of the same sulfonic acid gave no reaction, mainly due to no amine group activating the cyclohexanone *via* the enamine (entries 4 and 5).[13] Contrasting salt **5** with diamine derivative **4**, higher catalytic efficiency and asymmetric inductivity suggested that introduction of H^+ might form a more effective hydrogen bond by avoiding elongating the O···H distance which resulted from the quick inversion of the lone electron pair on the nitrogen atom of the primary amine (see Figure 5). In a control experiment, catalyst **6** gave no Michael addition adduct (entry 7), which showed that the amide unit might contribute to formation of a further hydrogen bond to activate the nitroalkene to some extent.

Table 2. The substrate generality.



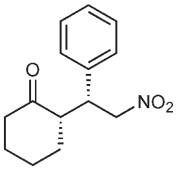
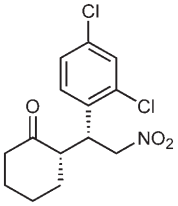
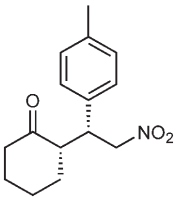
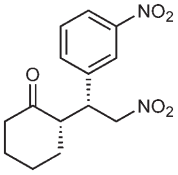
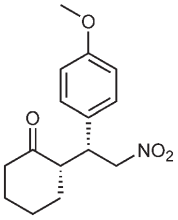
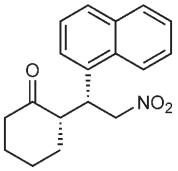
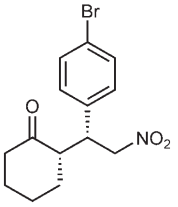
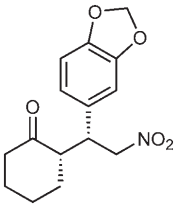
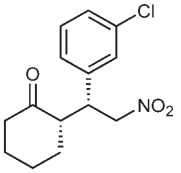
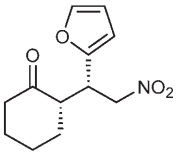
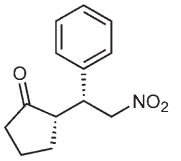
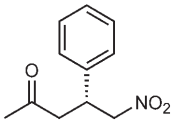
Entry	Products	Temperature [°C]	*t* [h]	Yield [%]	*dr* [*syn/anti*]	*ee* [%]
1		0	12	98	76:24	84
2		−20	36	80	82:18	87
3		0	12	99	87:13	94
4		−20	36	53	96:4	95
5		0	12	69	83:17	85
6		0	12	40	58:42	78
7		0	12	65	74:26	85
8		−20	36	86	80:20	93
9		0	12	82	88:12	92
10		−20	36	62	96:4	94
11		0	12	83	68:32	85
12		−20	36	65	70:30	88

Table 2. (Continued)

Entry	Products	Temperature [°C]	*t* [h]	Yield [%]	*dr* [*syn/anti*]	*ee* [%]
13		0	12	89	73:27	90
14		−20	36	68	87:13	95
15		0	12	74	70:30	85
16		0	12	87	61:39	61
17		0	12	52	83:17	83
18		0	12	57	–	69

Under the optimal conditions, a variety of nitroolefins with different structures were investigated, with the results being summarized in Table 4. Various styrene-type nitroolefins reacted smoothly with cyclohexanone in good yields with excellent diastereoselectivities and enantioselectivities (entries 1–11). Generally, substituents on aryl groups influenced only slightly the diastereoselectivities and enantioselectivities, as well as the yields. For example, nitroolefins bearing both electron-withdrawing and electron-donating aryl groups gave the desired products with high selectivities (*dr* up to 94/6 and *ee* up to 96%) in excellent yields (up to 99%). In the presence of an additional 50 μL of water, the reactivity and selectivity of the model reaction were maintained (entry 2). The observed diastereoselectivities and/or enantioselectivities for both cyclopentanone and acetone appeared to be higher than those obtained previously with a secondary amine as the catalyst (entries 12 and 13). While attempting to use cycloheptanone and α-tetralone as the prochiral donors, very poor reaction efficiencies were produced.

With regard to an interesting synthetic application of this protocol, and considering the absolute configuration of the chiral diamine moiety has little effect on the asymmetric inductivity (Table 3, entry 1 *vs.* 2), commercially cheap racemic 1,2-diphenylethane-1,2-diamine was directly used to synthesize the salt **7**. Catalyzed by salt **7**, the reaction of cyclohexanone and nitrostyrene provided almost the same yield of the product with little loss in terms of selectivities (Scheme 1). In order to explore the reason that the racemic diamine could not influence the reactivity and selectivities, the geometries of **(*R*,*R*)-4** and **(*S*,*S*)-4** were optimized by the B3LYP method using a 6-31G* basis set (Figure 6).[14] Although the two phenyl groups of the diamine moieties were respectively bent outwards and inwards in **(*R*,*R*)-4** or inwards and outwards in **(*S*,*S*)-4**, the structures of their two amino acid units remained similar and the N···N distance of two active sites respectively remained 5.09 Å in **(*R*,*R*)-4** and 5.56 Å in **(*S*,*S*)-4**. This approximation could make them provide a similarly efficient cooperation in the Michael addition of ketone to nitroolefin. Thus, differing from our previous studies using diamine derivatives as catalysts, in which the spread of the phenyl group of the diamine moiety directly dominated the face selectivity,[11,15] the phenyl groups in **(*R*,*R*)-4** or **(*S*,*S*)-4** contributed to the highly asymmetric induction only by furnishing an appropriate chiral

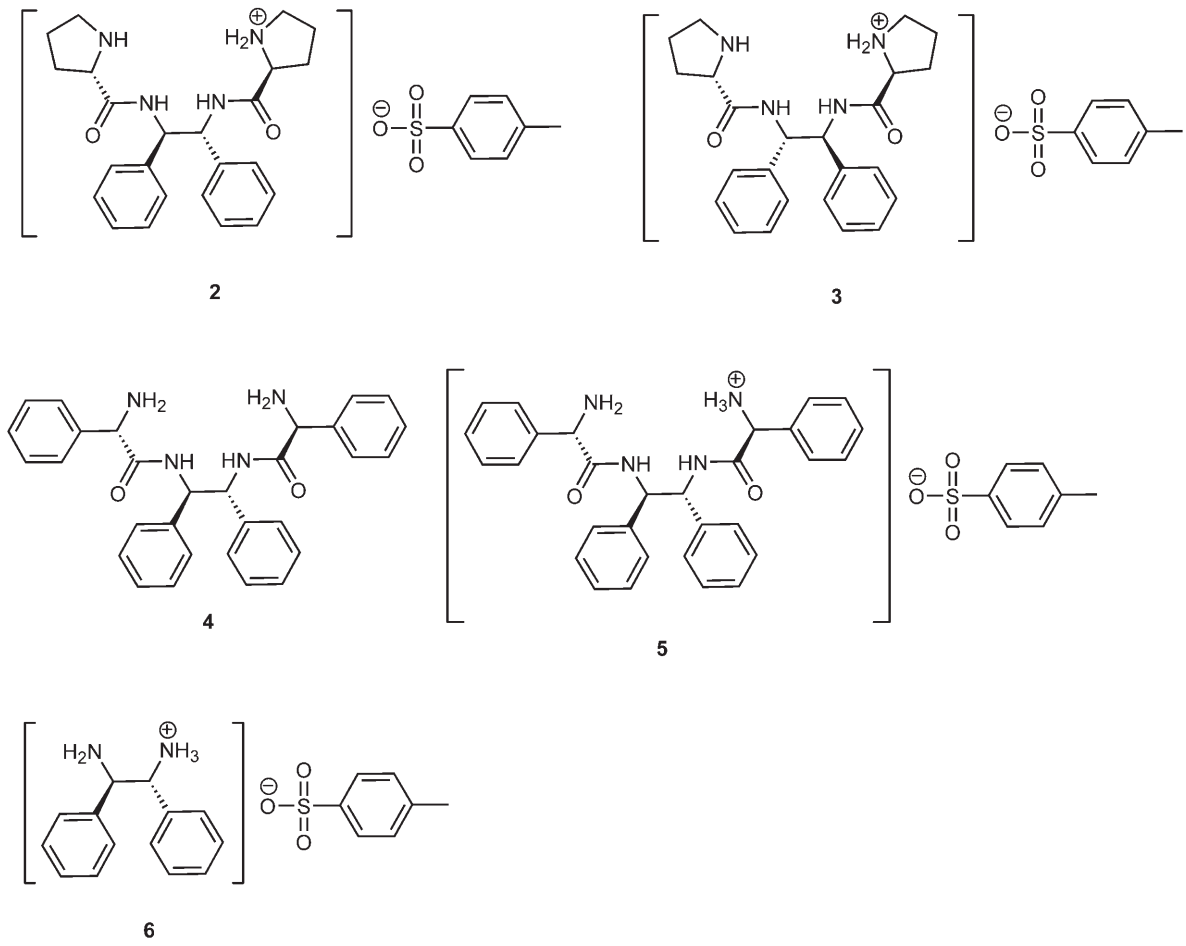
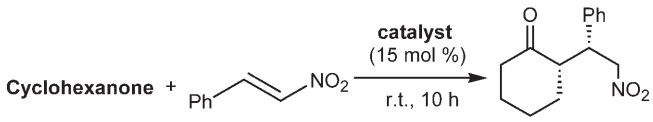


Figure 4. The evaluated chiral cation catalysts.

Table 3. Optimization studies.



Entry	Catalyst	Yield [%][a]	*dr* [*syn*/*anti*][b]	*ee* [%][c]
1	**2**	90	95:5	70
2	**3**	83	96:4	72
3	**4**	58	87:13	74
4[d]	**4**	94	90:10	90
5[e]	**4**	n.r.	-	-
6	**5**	91	93:7	93
7	**6**	n.r.	-	-

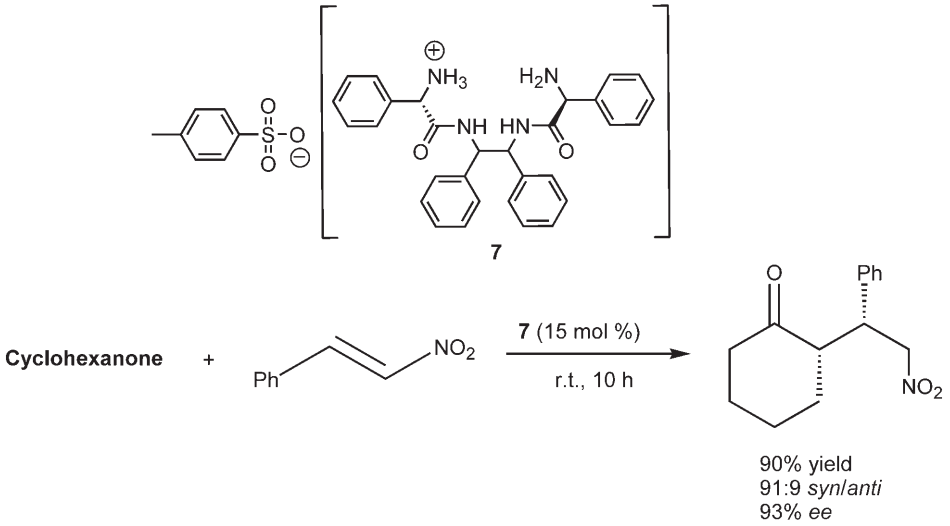
[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by HPLC analysis.
[d] 4-Toluenesulfonic acid (5 mol%) was added.
[e] 4-Toluenesulfonic acid (30 mol%) was added. n. r. = no reaction.

pocket with the amino acid units and an appropriate distance between the two active sites.

A catalytic cycle consistent with our experimental observations was proposed and is depicted in Figure 7. The nitroalkene is activated through two oxygen atoms binding respectively to hydrogen atoms on amide and $-NH_3^+$ groups,[16] and the cyclohexanone condenses with the primary amine group of catalyst **5** to form imine intermediate **A**. Isomerization of imine **A** leads to the formation of active enamine **B**,[7] which can react with the electrophilic nitroalkene *via* nucleophilic addition to give an α-modified iminium ion **C**. After H^+ transfers to form imine **D**, imine **D** can hydrolyze to give Michael addition adduct in the presence of water. In contrast to secondary amine-catalyzed Michael additions of ketones to nitroolefins, which proceed through iminium ion, enamine to iminium ion in tandem,[7] the primary amine-catalyzed reaction proceeds *via* imine **A**, enamine **B**, and iminium ion **C** to imine **D**.

Chiral Cation-Chiral Anion Salt Catalysis

Chiral anion salt **1f** and chiral cation salt **5**, respectively, have been successfully employed to the Mi-



Scheme 1.

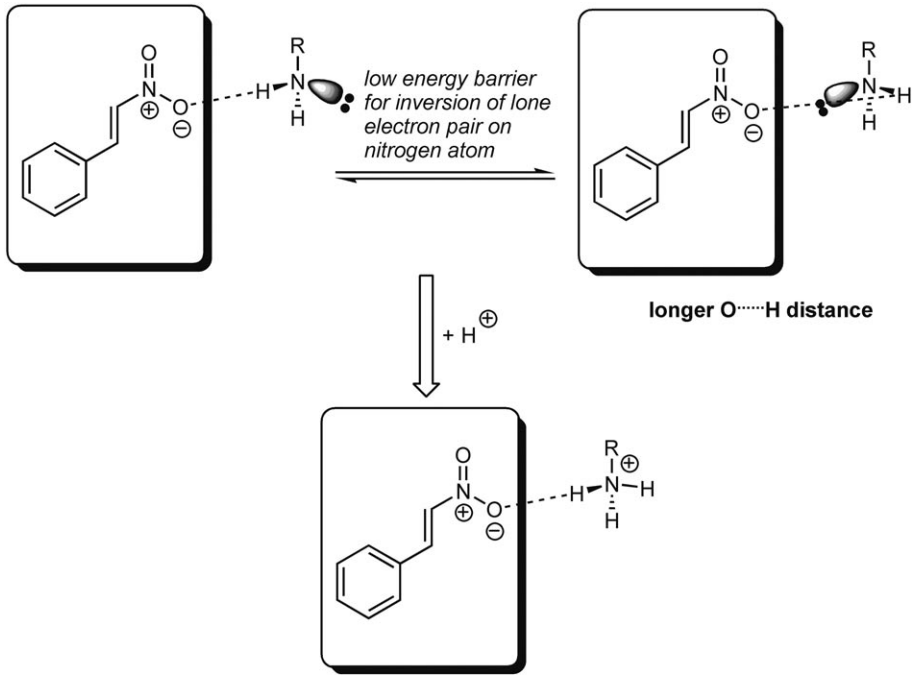


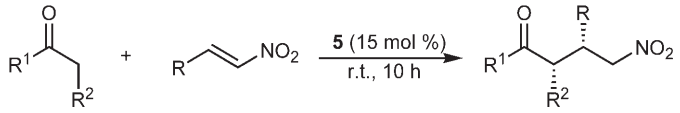
Figure 5. Proposed effect of the amine protonation process on the hydrogen bond.

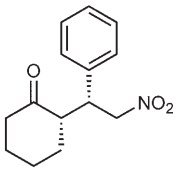
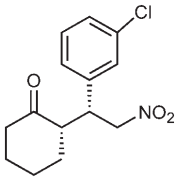
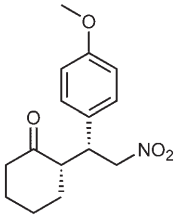
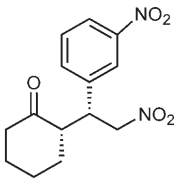
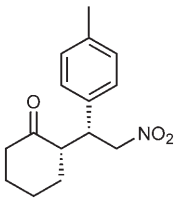
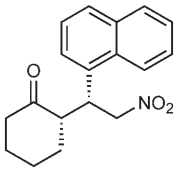
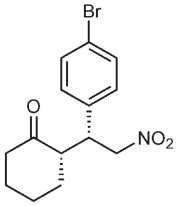
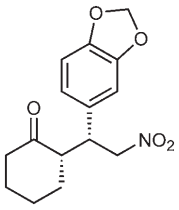
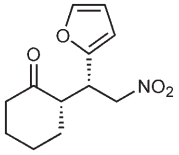
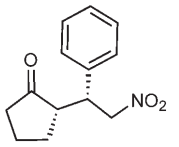
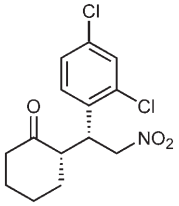
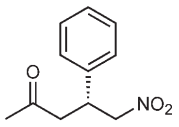
chael addition of ketones to nitroolefins, which revealed that the combination[17] of a chiral cation and a chiral anion might produce strong asymmetric induction. The 4-toluenesulfonic acid anion of catalyst **5** was replaced with the chiral D-camphorsulfonic acid anion to form a chiral cation-chiral anion salt catalyst **8**. Catalyst **8** also afforded 2-(2-nitro-1-phenyl-ethyl)-cyclohexanone in 95% yield with 93:7 *syn*/*anti* and 93% *ee* (Scheme 2).

Conclusions

The primary amine-salt catalysis has been applied to the asymmetric Michael addition of ketones to nitroolefins. Chiral functionalized salts, type **I**, such as potassium (*S*)-2-amino-2-(4-chlorophenyl)acetate **1f**, type **II**, such as **5**, and type **III**, such as **8**, could effectively promote the Michael addition of ketones to nitroolefins. The experimental procedures were air-tolerant, simple and convenient. Amino acid salt **1f** possessed remarkable advantages: cheap, readily pre-

Table 4. The substrate generality.



Entry	Product	Yield [%]	*dr* [*syn*/*anti*]	*ee* [%]	Entry	Product	Yield [%]	*dr* [*syn*/*anti*]	*ee* [%]
1		91	93:7	93	8		99	91:9	95
2[a]		91	94:6	92					
3		95	91:9	91	9		99	90:10	96
4		99	92:8	95	10		88	94:6	95
5		99	90:10	94	11		88	92:8	96
6		99	91:9	94	12		99	80:20	93
7		99	94:6	96	13		99	-	73

[a] Water (50 μL) was added.

pared and efficiently recovered. By dual activation catalysis, chiral positive ion ammonium salt **5** gave the corresponding products in excellent yields (≥88%) with selectivities (up to 94:6 *syn*/*anti* and 96% *ee*) in no more than 10 h. Optimizing conditions revealed that $-NH_3^+$ cooperating with an amide could provide more effective hydrogen bond interactions than $-NH_2$ to activate the acceptor, to attain sufficient proximity for carbon-carbon bond formation. These protocols provide an alternative to that of the processes with secondary amine (e.g., pyrrolidine- and imidazoline-type) chiral organocatalysts. Further attempts to improve the selectivity and catalytic efficiency through modifying the catalyst and optimizing the reaction conditions, whilst exploring the origins of the selectivity, are underway.

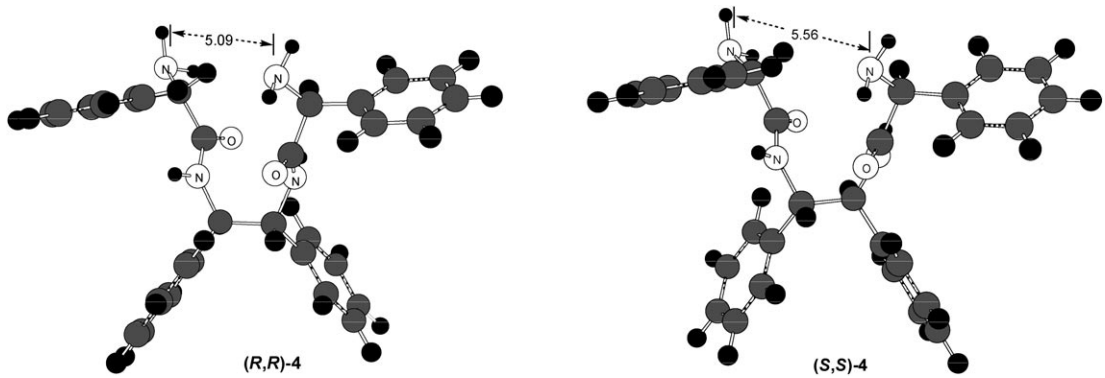


Figure 6. The optimized geometries of **(*R*,*R*)-4** and **(*S*,*S*)-4** at B3LYP/6-31G(d) level.

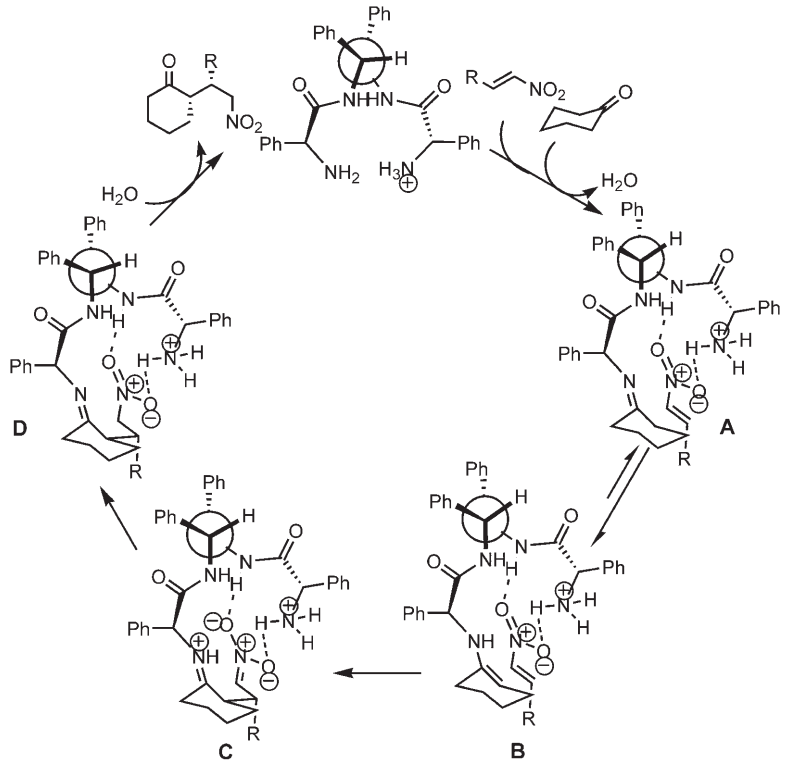


Figure 7. The proposed mechanism (anion TsO^- was omitted).

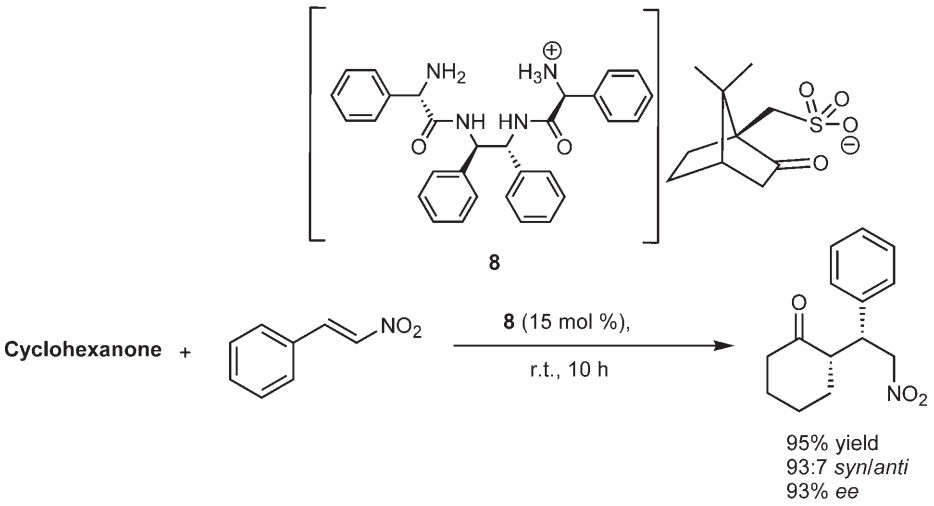
Experimental Section

General Remarks

Michael addition reactions were carried out in test tubes with magnetic stirring and no special precautions were taken to exclude water or air from the reaction vessel. Cyclohexanone and *m*-xylene were purified by the usual methods. Purification of reaction products was carried out by flash chromatography using silica gel. Optical rotations were measured with a sodium lamp and reported as follows: $[\alpha]_D^T$: (c = g/100 mL, solvent). ^{1}H NMR spectra were recorded on instruments of 300 MHz. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, $\delta = 7.26$). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), integration, and assignment. Enantiomer ratios were determined by chiral HPLC analysis on Daicel Chiralcel AS-H and AD-H.

Typical Procedure for the Synthesis of (2S,2′S)-N,N′-((1R,2R)-1,2-Diphenylethane-1,2-diyl)bis(2-amino-2-phenylacetamide)

(2*S*,2′*S*)-*N*,*N*′-((1*R*,2*R*)-1,2-Diphenylethane-1,2-diyl)bis(2-amino-2-phenylacetamide) were prepared referring to our previous method[11].



Scheme 2.

Typical Procedure for the Synthesis of 2-(2-Nitro-1-phenylethyl)cyclohexanone

Procedure for amino acid salt catalysis: To the mixture of potassium (*S*)-2-amino-2-(4-chlorophenyl)acetate **1f** (4.5 mg, 0.02 mmol) and (2-nitrovinyl)benzene (14.9 mg, 0.1 mmol) in *m*-xylene (0.2 mL) was added cyclohexanone (0.2 mL) at 0 °C. The mixture was stirred for 12 h and purified by flash chromatography using EtOAc/PE (1:10, v/v) as eluent to afford 2-(2-nitro-1-phenylethyl)cyclohexanone as an white solid; yield: 24.2 mg (98 %, 76:24 *syn*/*anti*, 84 % *ee*).

Procedure for ammonium salt catalysis: To the mixture of (2*S*,2′*S*)-*N*,*N*′-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(2-amino-2-phenylacetamide) (7.2 mg, 0.015 mmol) and 4-toluenesulfonic acid (2.6 mg, 0.015 mmol) was added cyclohexanone (0.2 mL) at room temperature. After stirring for 20 min, nitrostyrene (14.9 mg, 0.1 mmol) was added. The mixture was stirred for 10 h at room temperature and purified by flash chromatography using EtOAc/PE (1:10, v/v) as eluent to afford 2-(2-nitro-1-phenylethyl)cyclohexanone as a white solid; yield: 22.5 mg (91 % yield, 93:7 *syn*/*anti*, 93 % *ee*). HPLC (Chiralcel AS-H, hexane/*i*-PrOH, 75:25 *v*/*v*, 1.0 mL min^{-1}, 23 °C, UV 210 nm): t_r (minor) = 9.30 min, t_r (major) = 13.19 min; $[\alpha]_D^{25}$: −21.9° (*c* 0.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 3H), 7.18–7.15 (m, 2H), 4.94 (dd, J_1 = 12.5 Hz, J_2 = 4.6 Hz, 1H), 4.63 (dd, J_1 = 12.5 Hz, J_2 = 9.9 Hz, 1H), 3.76 (dt, J_1 = 9.9 Hz, J_2 = 4.6 Hz, 1H), 2.73–2.68 (m, 1H), 2.50–2.38 (m, 2H), 2.10–2.05 (m, 1H), 1.81–1.53 (m, 4H), 1.25–1.20 (m, 1H).

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[13] Other anions such as CH_3COO^-, CF_3COO^- and $CH_3SO_3^-$ were also investigated with either inferior results or complete failure of the reaction observed.

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