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PAPER

Chiral phosphoproline-catalyzed asymmetric Michael addition of ketones to nitroolefins: an experimental and theoretical study†

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A novel pyrrolidine-based chiral phosphoproline is an effective bifunctional organocatalyst for the asymmetric Michael addition of ketones to nitroolefins giving high levels of *diastereo*- and *enantio*-selectivities (up to > 99 : 1 dr and 96% ee). ***anti*-SR** Transition state has the lowest barrier which controls the stereoselectivity, in agreement with experimental results.

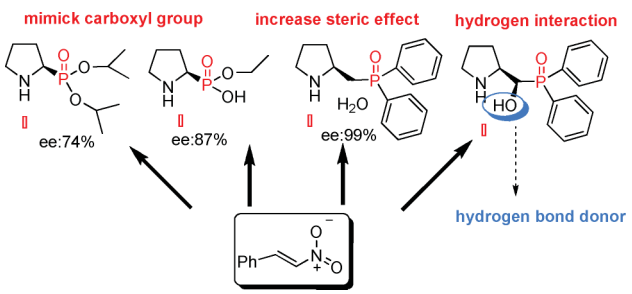
Introduction

During recent years, organocatalysis has developed rapidly and much attention has been given extensively to the design and application of organocatalysts to construct asymmetric carbon-carbon and carbon-heteroatom bonds for the preparation of enantiomerically pure compounds.[1]

Among well-developed methods, the asymmetric Michael addition of different carbon-centered nucleophiles to electron deficient nitroolefins is widely recognized as one of the most important and versatile methods for the formation of carbon-carbon bonds with high diastereoselectivities as well as high enantioselectivities for the formation of two contiguous stereocentres in a single step.[2] Because of the versatile reactivity of the nitro group, the resulting nitroalkanes can readily be transformed into versatile synthetic building blocks, such as amines, nitrile oxides, ketones, and carboxylic acids.[3] As a result, the design and development of new and efficient chiral organocatalysts to achieve high levels of enantio- and/or diastereoselectivity in Michael conjugate additions remains a strong challenge in synthetic organic chemistry.[4]

Pioneering work by Hanessian,[5] List,[6] Ender,[7] Alexakis,[8] and Ley[9] has served to show that (*S*)-proline is a very good catalyst for asymmetric Michael addition reactions, the key step being the formation of an enamine intermediate. Because of the poor solubility of proline in many organic solvents, numerous novel proline derivatives have been developed and used as excellent organocatalysts.

The pyrrolidine ring of these compounds is now regarded as one of the "privileged" backbones for asymmetric catalysis.[4i] Further investigations and applications have been made with water as an additive or reaction solvent,[10] and this may indicate that a hydrogen-bond donor function is valuable catalyst structure. To the best of our knowledge, there has been only a few pyrrolidine-type organocatalysts having a phosphine oxide function linked to the "privileged" chiral pyrrolidine to be used successfully[4c,4e,11] (Scheme 1). It has been suggested that its P═O group (compound I, II) may mimic a carboxyl group and interact favourably with the nitro group by dipole interactions mediate by a single water molecule (compound III) and thereby control both enantio- and diastereo-selectivity.[4c] However, these organocatalysts still have some drawbacks, such as high catalyst loading (10–30 mol %) and low reaction temperature, which will limit their application in the pharmaceutical industry. We have therefore sought to improve the performance of the diphenyl-pyrrolidyl-methyl-phosphine oxide catalyst through the introduction of a chiral functional group hydroxyl, as shown (Scheme 1, IV).



Scheme 1 Structure comparison of designed catalysts.

This catalyst design has a hydroxyl group introduced as an intramolecular hydrogen bond donor for activation of the nitro group to replace the water molecule described in Zhong's work.[4c] We here report the asymmetric Michael addition of cyclic ketones

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to nitroolefins promoted by this simple bifunctionalorganocatalystusing low catalyst loading (5 mol %) in solvent-free reactions, and achieving high levels of diastereo- and *enantio*-selectivity. In addition, we have sought to explain these results using a DFT theoretical study.

Experimental

Synthesis of the catalyst

Synthesis of the compound 3SR

A solution of **1** (24 mmol, 4.776 g, yellow oil) in dichloromethane (30 mL) was treated dropwise with 2 (28.8 mmol, 5.820 g, solid) and triethylamine (2 mL). The reaction was monitored by TLC until the compound 1 had disappeared. Solvent was then removed under reduced pressure to give a white solid, purified by multi-recrystallization in ethyl acetate to give product **3SR** (5.144 g) as a colorless amorphous solid (yield 54%).

Synthesis of the compound 4

Compound **3SR** (2.5 mmol, 1.000 g, white solid) in methanol (30 mL) was treated dropwise with concentrated hydrochloric acid (2 mL) with ice cooling. The reaction was monitored by MS until the reactant **3SR** vanished. Solvent was then removed under reduced pressure to give **4** as a white solid (0.710 g, 91%).

Synthesis of the compound 5

Compound **4** (1.0 mmol, 0.300 g, white solid) was added in a 50 mL flask containing 10 mL water, and then potassium carbonate (10 mmol, 0.560 g, solid) and quinoline-8-sulfonyl chloride (2.0 mmol, 0.460 g, solid) was added to this solution, and then 10 mL CH_2Cl_2 was added to solute the quinoline-8-sulfonyl chloride. The reaction was tracked by TLC until the reactant vanished. The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2–MeOH (20 : 1) to give compound **5** (452 mg, 0.92 mmol, 92%) as a white solid.

General experimental procedure for the Michael addition

The *trans*-nitrostyrene (38 mg, 0.25 mmol, 1 eq) in solution in cyclohexanone (0.52 mL, 5 mmol, 20 eq) was treated with catalyst **4** (4 mg, 0.0125 mmol (5 mmol %), 0.050eq) in the presence of *p*-nitrobenzoic acid (0.025 mmol, 0.010 eq) and KOH (50 µL 1 M). The resulting mixture was stirred at r. t.. After the reaction was complete (monitored by TLC), the mixture was purified by flash chromatography (hexane : EtOAc = 9/1) to give the product.

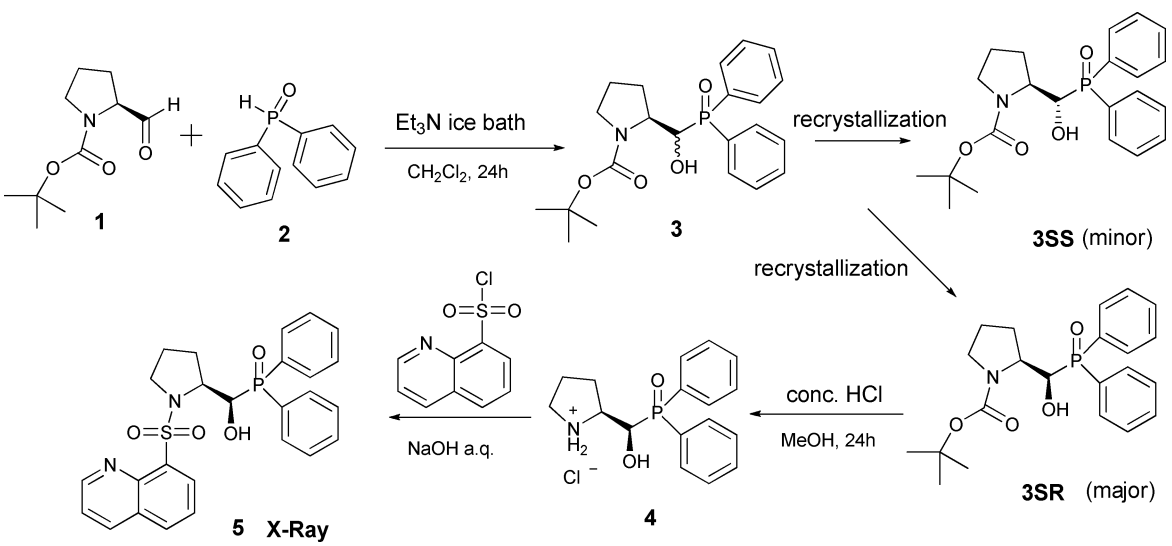
Computation details

All the geometries were fully optimized with GAUSSIAN[12] at the B3LYP/6-31G* level followed by frequency calculations to determine the nature of the stationary points. The reported energies come from the gas phase on the DFT gas-phase geometries.

Results and discussion

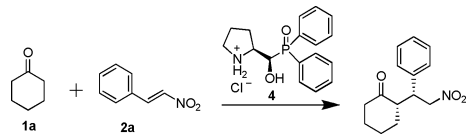
Synthesis of the catalyst

The newly designed *S*-2-[*R*-(diphenyl-phosphinoyl)-hydroxy-methyl]-pyrrolidinium chloride **4** was easily prepared from *S*-2-acetyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester **1** as its hydrochloride salt (Scheme 2). First, compound **1** was coupled with diphenylphosphine oxide **2**, to give *S*-2-(diphenylphosphanyl-hydroxy-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **3** as a mixture of epimers. Subsequently, through multi-recrystallization of **3**, one chiral pure stereoisomer **3SR** was obtained. Finally, the **Boc** protect group was removed using concentrated HCl and MeOH to give **4** as the hydrochloric acid salt of the newly designed pyrrolidine-hydroxyl phosphine oxide. The absolute configuration of **4** was determined by X-ray diffraction of the derived *R*-(diphenyl-phosphinoyl)-[*S*-1-(quinoline-8-sulfonyl)-pyrrolidin-2-yl]-methanol **5** which was readily crystallized from ether/ethyl acetate (see ESI†). Because **4**



Scheme 2 Synthesis of catalyst **4**.

Table 1 Variation in base and temperature for reaction of cyclohexanone with *trans*-nitrostyrene[a]



Entry	Temp.[°C]	Time [h]	KOH[b] [mmol]	Yield[c] [%]	dr[d]	ee[e] [%]
1	r. t.	115	0	n. d.		
2	r. t.	115	0.025	trace		
3	r. t.	57	0.050	85	88 : 12	90
4	r. t.	57	0.075	75	96 : 4	86
5	r. t.	57	0.100	94	94 : 6	88
6	50	19	0.050	94	90 : 10	83
7	50	19	0.075	89	92 : 8	82

[a] Unless otherwise noted, all the reactions were carried out by using *trans*-β-nitrostyrene (0.25 mmol, 1.0 equiv) and cyclohexanone (5 mmol, 20 equiv) in the presence of 0.05 mmol of catalyst (20 mol%). [b] Concentration of KOH is 1 M. [c] Isolated yield. [d] Determined by ^{1}H-NMR of the crude mixture. [e] Determined by chiral HPLC analysis (Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 mL min^{-1}).

decomposed slowly on storage as the free base, it was kept as its hydrochloric acid salt and converted into the free base *in situ* for catalysis by addition of a base such as **1** M KOH solution.

The screening of the catalytic condition

With the catalyst to hand, a preliminary examination was carried out on the reaction of β-nitrostyrene with cyclohexanone. First, the result of variations in base and reaction temperature is shown in Table 1. The addition of 1 M KOH aqueous solution was found to be an essential factor for this reaction (Table 1, entry 1–5). It could be seen that addition of 50 μL 1 mol L^{-1} KOH (0.050 mmol) gave out the best enantioselectivity (ee), diastereoselectivity (dr) and reasonable chemical yield (Table 1, entry 3). In this case, the amount of KOH just neutralized the acidity of itself 20 mol% catalyst, so it could accelerate the Michael addition smoothly. There was no any benefit to the ee value by increasing the amount of inorganic base because the KOH used in large excess could also promote cyclohexanone coupling with the nitroolefins even without the assistance of catalyst in the free base. Interestingly, when the base was not enough to neutralize the acidity of catalyst, no reaction progress was detected even to prolong its reaction time (Table 1, entry 1–2). In order to shorten the reaction time and keep good chemical yield of our product, we tried to push the temperature from room temperature to 50° C, however, it was a pity that the ee value of product dropped from 90% to 83% sharp.[13]

It is worth mentioning that, thus far, for some reported nitro-Michael additions, a suitable Brønsted acid must be used as a cocatalyst.[14] A survey of eight acidic cocatalysts revealed that the acidic cocatalyst had an important influence on the reaction (Table 2, entry 1–8).

The addition of 10 mol % carboxylic acid as a cocatalyst significantly promoted the Michael addition and enhanced the selectivity relative to the catalyst in the absence of an acidic cocatalyst (Table 2, entry 6–8). Higher enantioselectivity was observed for *p*-nitrobenzoic acid (Table 2, entry 8, 94% ee), benzoic acid (Table 2, entry 7, 94% ee), and *p*-methylbenzoic acid (Table 2, entry 6, 92% ee). Considering both the yield and enantioselectivity

Table 2 Screening of the Additive[a]

Entry	Time [h]	Adduct[b] [10 mol%]	Yield[c] [%]	dr[d]	ee[e] [%]
1	71	4-ClC_6H_4COOH	99	94 : 6	85
2	71	4-$CF_3C_6H_4CH_2COOH$	98	97 : 3	86
3	71	2-$NO_2C_6H_4COOH$	84	86 : 13	87
4	71	4-$NO_2C_6H_4CH_2COOH$	98	98 : 2	87
5	71	4-HOC_6H_4COOH	87	97 : 3	89
6	71	4-$CH_3C_6H_4COOH$	94	96 : 4	92
7	71	C_6H_5COOH	64	94 : 6	94
8	71	4-$NO_2C_6H_4COOH$	92	94 : 6	94

[a] Unless otherwise noted, all the reactions were carried out at room temperature by using *trans*-β-nitrostyrene (0.25 mmol, 1.0 equiv) and cyclohexanone (5 mmol, 20 equiv) in the presence of 50 μL of 1 M KOH solution (0.05 mmol). [b] The amount of additive is 10 mol%. [c] Isolated yield. [d] Determined by ^{1}H NMR of the crude mixture. [e] Determined by chiral HPLC analysis (Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 mL min^{-1}).

of the product, *p*-nitrobenzoic acid was the best choice as the acid cocatalyst. Next, we investigated the influence of catalyst loading on the reaction outcome (Table 3, entry 1–8). A reduction in the amount of catalyst **4** from 20 to 5 mol% resulted in a relatively slow reaction but still gave good chemical yield and excellent dr and ee (Table 3, entry 8). Increasing the amount of 1 M KOH aqueous solution with 5 mol% catalyst **4** and 10 mol% *p*-nitrobenzoic acid was predominantly beneficial for chemical yield with a longer reaction time (Table 3, entry 5–8). Under the optimal reaction conditions (5 mol% catalyst, 10 mol% *p*-nitrobenzoic acid, 50 μL 1 M KOH (0.050 mmol), at r.t., solvent effect was taken into consideration. Unfortunately, all these experiments were disappointing giving poor conversions. Therefore all reactions were carried out in neat solution of cyclohexanone in large excess (20 eq).

We also had a test to lower the molecular ratio of cyclohexanone from 20 equivalents to 10 equivalents. The reaction was elongated to an unreasonable time. And the yield of this reaction became very low. So it is inadvisable to reduce the use of cyclohexanone (20 equivalents).[3,13a,15]

The scope of the substrate of this catalytic reaction

With optimized reaction conditions established, we probed the scope of the reaction with a variety of substituted *trans*-β-nitrostyrenes to establish the broader utility of this asymmetric transformation. The results are summarized in Table 4.

The results (Table 4) show that the nature of the substituents on the aryl group slightly influenced the enantioselectivity and diastereoselectivity except the yield. For nitrostyrenes with methyl group at different position of benzene ring, the reaction proceeded smoothly to afford Michael adduct (Table 4, entry 2–4) in good *enantio*-(92–96% ee) and diastereoselectivity (*syn*/anti = 92 : 8), especially for methyl group at *ortho*- and *meta*-position.

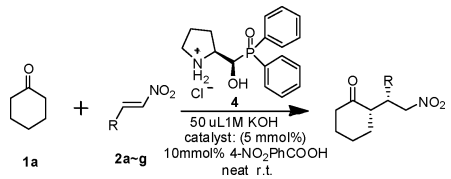
The reactions of the benzene ring substituents at *para*-position were also studied systematically. When substituted for the strong electron-donating groups such as methoxyl group, the entire catalytic reaction would greatly reduce the yield even that no reaction occurs in this situation. When substituted for the strong electron-withdrawing group such as fluorine and chlorine atom (Table 4, entry 5–6), both the yield and the ee value would be greatly improved. Unfortunately, the point was that this series

Table 3 Screening of the loading of catalyst **4**[a]

Entry	Cat.[mmol%]	Time [h]	KOH[b] [mmol]	Yield[c] [%]	dr[d]	ee[e] [%]
1	20	71	0.05	92	94 : 6	94
2	15	71	0.0375	98	85 : 15	81
3	10	71	0.025	79	89 : 11	92
4	5	71	0.0125	46	89 : 11	95
5	5	159	0.0125	74	92 : 8	94
6	5	159	0.025	89	90 : 10	94
7	5	159	0.0375	84	91 : 9	95
8	5	159	0.050	82	92 : 8	96

[a] Unless otherwise noted, all the reactions were carried out at room temperature by using *trans*-β-nitrostyrene (0.25 mmol, 1.0 equiv) and cyclohexanone (5 mmol, 20 equiv) in the presence of 10 mol % 4-$NO_2C_6H_4COOH$. [b] The concentration of KOH is 1 M. [c] Isolated yield. [d] Determined by ^{1}H NMR of the crude mixture. [e] Determined by chiral HPLC analysis (Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 mL min^{-1})

Table 4 Michael addition reactions of neat cyclohexanone to *trans*-nitroolefins using catalyst **4**[a]



Entry	Ar		Time [h]	Yield[b] [%]	dr[c]	ee[d] [%]
1	Ph	**3a**	7d	82	92 : 8	96
2	4-MePh	**3b**	17d	88	92 : 8	92
3	3-MePh	**3c**	17d	91	92 : 8	96
4	2-MePh	**3d**	20d	87	93 : 7	95
5	4-FPh	**3e**	17d	99	90 : 10	94
6	4-ClPh	**3f**	7d	87	92 : 8	91
7	2-ClPh	**3g**	7d	94	99 : 1	96
8	2-BrPh	**3h**	7d	91	99 : 1	96
9	Furanyl	**3i**	20d	93	82 : 18	91

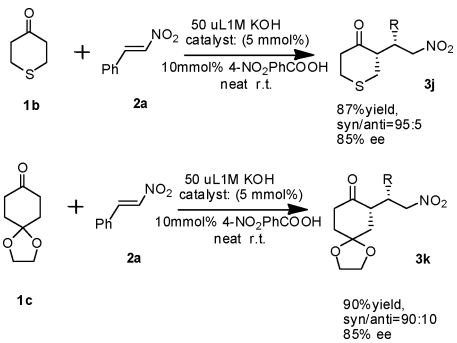
[a] Unless otherwise noted, all the reactions were carried out at r.t. using nitrostyrene (0.25 mmol, 1.0 equiv) and cyclohexanone (5 mmol, 20 equiv) in the presence of 10 mmol% 4-$NO_2C_6H_4COOH$ and 50 μL1 M KOH. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by chiral HPLC analysis (Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 mL min^{-1}).

of substituted substrate did not get the best ee value. *Ortho*-substituted electron-withdrawing groups such as 3-chloro- and 3-bromo- substituted substrates (Table 4, entry 7–8), could be a very good dr value of products with ee values. Finally, substituted heterocyclic substrate (Table 4, entry 9) can also get good ee values.

The asymmetric additions of other ketones to nitrostyrene **2a** with the use of **4** as a catalyst were also preliminarily investigated. As shown in Scheme 3, other cyclic ketones such as tetrahydrothiopyran-4-one **1b** and cyclohexane-1,4-di-one monoethyleneacetal **1c** also reacted smoothly with **2a** at room temperature, and the diastereoselectivity of these products were maintained although the ee value (85%) of the product was greatly reduced.

The computational study of the catalytic mechanism

On the basis of the experimental results, a mechanism based upon catalyst **4** is proposed to account for the observed diastereo- and enantioselectivity. As shown in Fig. 1, the free base of our catalyst behaves as a bifunctional catalyst. The pyrrolidine ring



Scheme 3 Reaction of the other ketones.

first reacts with the carbonyl group of cyclohexanone to form an enamine with the help of the acidic cocatalyst. Subsequently, the proton of the hydroxyl group would orientate the nitro group through hydrogen-bonding interaction so that enamine acted as a nucleophile and attacked the nitroolefin from different faces to give the corresponding *enantio*- and diastereo-selective products. The relative energies of the different transition states or intermediates are given in Fig. 1.

The lowest energy transition states leading to the four products from the reactions of the enamine of cyclohexanone with the (*E*)-(2-nitrovinyl)benzene were shown in Fig. 1. The transition states involving the **Re** attack on the anti-enamine (**anti-SSts**, **anti-SRts**) were lower in energy than that involving **Si** attack on the *syn*-enamine (***syn*-RRts**, ***syn*-RSts**) as shown in Fig. 1. Favourable hydrogen bonding interaction between the hydroxyl group of catalyst **4** and the nitro group of (*E*)-(2-nitrovinyl)benzene contributed to further electrostatic stabilization of all of the transition states.

Transition state **anti-SSts** was slightly destabilized due to the eclipsed conformation from the forming C–C bond (see the Newman projections in the ESI, Figure S2†), and the phenyl group easily adopted a relatively sterically hindered arrangement in this eclipsed conformation. Fortunately, this transition state composed the strongest hydrogen bond with the shortest distance 1.668 Å to stabilize the orientation of β-nitroolefins.

However, in transition state **anti-SRts** (see Fig. 2, Figure S1†), the conformation was changed from eclipsed to staggered, which sufficiently released the steric repulsion of the phenyl group. So the activation energy dropped to 4.9 kcal mol^{-1}, which was the lowest barrier of all the transition states. That meant its corresponding compound was the main product of our asymmetric catalytic

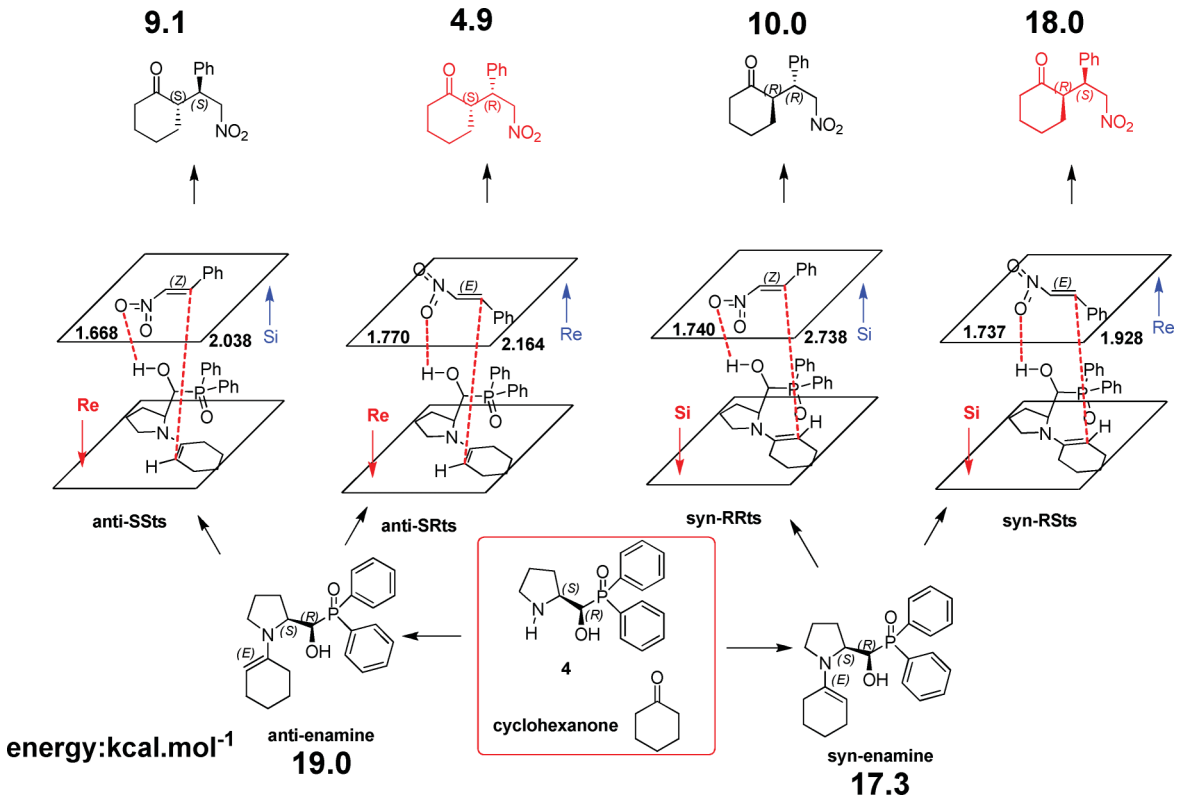


Fig. 1 Transition state geometries for the reaction of *syn*- and *anti*-enamine with (*E*)-(2-nitrovinyl)benzene.

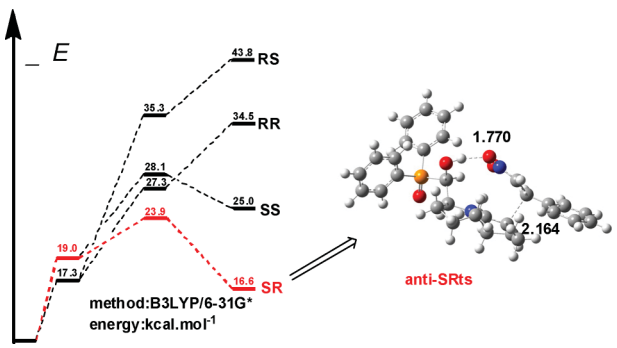


Fig. 2 Schematic energy profile of four stereoselective products (*RS*, *RR*, *SS*, *SR*) for this organocatalytic mechanism.

reaction. This explanation was consistent with the experimental results. It was worth noting that the pathways involving the *anti*-enamine were both exothermic reactions thermodynamically. On the contrary, both the reactions involving the *syn*-enamine were endothermic, which meant the products were energy-unfavorable according to the computed geometries (see Fig. 2). In the second hand, the activation energy of both transition states were quite high (10.0 kcal mol^{-1} and 18.0 $kcalmol^{-1}$) purely due to the steric hindrance of phenyl group though their conformation are both staggered (see Figure S3 and S4†).

Conclusion

We have developed a novel type of pyrrolidine-based catalyst bearing chiral phosphoproline functions, which works well as a bisfunctional organocatalyst to promote the asymmetric Michael addiction of ketones to nitrostyrenes. The reaction takes place smoothly with perfect diastereo- (up to >99 : 1 dr) and high enantioselectivity (up to >96% ee) in the presence of a low loading of this catalyst (5 mol%). This can provide a potential useful method for the preparation of enantiomerically enriched γ-nitroketones. Further investigations on the application of this catalyst in asymmetric catalysis are in progress.

Acknowledgements

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