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ARTICLE TYPE

Asymmetric Michael addition of ketones to nitroolefins: Pyrrolidinyl-oxazole-carboxamides as new efficient organocatalysts

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Chiral pyrrolidinyl-oxazole-carboxamides were synthesized and used as efficient new organocatalysts for the asymmetric Michael addition of ketones with nitroalkenes under solvent-free conditions. Gratifyingly, the corresponding Michael adducts was obtained in higher yields (up to 99%) and excellent stereoselectivities (up to > 99/1 *dr* and 99% *ee*). Transition state models have been proposed to account for the high enantio- and diastereoselectivity of these Michael addition reactions and also the energetics have been investigated using density functional methods. These results support the preferential formation of *syn*-products by the approach of *trans*-β-nitrostyrene through the *re*-face of *anti*-enamine.

Introduction

In the past few years, a tremendous development has been witnessed in asymmetric organocatalysis reactions because of its potential applications in the synthesis of various New Chemical Entities (NCE).[1,2] In this regard, a number of primary and secondary chiral amine derivatives have been developed for a wide range of asymmetric synthesis, especially for the enatioselective transformation of carbonyl compounds into the corresponding adducts like, γ-nitrocarbonyls,[3] Mannich[4] and aldol type products.[5] However, the asymmetric Michael addition of ketones with nitroolefins as a key step in the preparation of various chiral molecules have received much attention due to versatile reactivity of the nitro functionality. The corresponding γ-nitrocarbonyls could be readily converted into a wide range of synthetically valuable products, such as amines,[6] nitrile oxides,[7] carboxylic acids,[8] ketones[8] and other functionalities. The organocatalytic asymmetric Michael addition of ketones with nitroolefins were developed by List[9] and Barbas,[10] independently. Since then, the interest in the area of asymmetric Michael addition has increased effectively and various useful organocatalysts have been extensively developed, such as modified L-proline,[11] chiral diaime,[12] pyrrolidine based diamine,[13] cinchona alkaloids-based bifunctional organocatalysts,[14] chiral guanidine,[15] and urea or thiourea-based bifunctional organocatalysts.[16]

Among the existing chiral organocatalysts, L-proline and other secondary amines like pyrrolidine based catalysts with bifunctional motif were proven to be more efficient in asymmetric synthesis.[17] The five-membered cyclic secondary amine structure of pyrrolidine is considered to be "crucial" as it activates the carbonyl compounds by the formation of the enamine intermediates.[18] Pyrrolidine organocatalysts in combination with other functional groups, such as chiral sulfonamide,[19] diarylprolinols[20] and the corresponding amides[21] were also proven that bifunctional molecules can catalyze a variety of asymmetric transformations.[19a,b, 22]

Stimulated by the results of Kokotos's pyrrolidine-thiohydantoins **1**,[23] Tang's thiourea-secondary amines[24] **2** and Wang's pyrrolidine sulfonamides[25] **3** (Fig. 1), and with an effort to search for new and efficient organocatalysts, we have developed some bifunctional organocatalysts by combining the pyrrolidine with oxazole ring via amide linkage as shown in Figure 1.

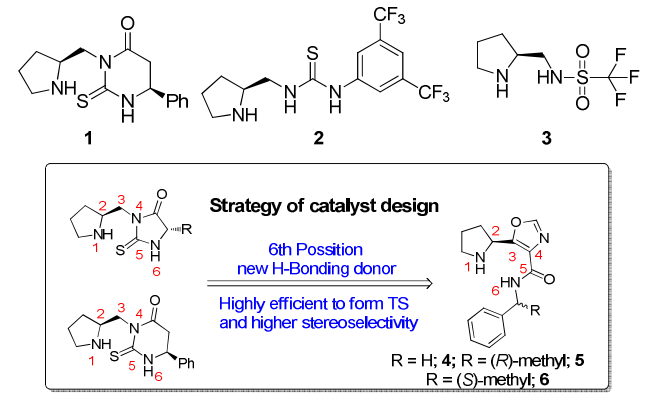

Fig. 1 A variety of pyrrolidine-based organocatalysts **1–3** and newly designed catalysts **4–6**.

Results and discussion

The rationale behind the design of new chiral catalysts was illustrated in Figure 1. To build a pyrrolidine based organocatalyst, apart from pyrrolidine ring there should be a hydrogen bond donating group (preferably at 4th and 6th or at either of the place from pyrrolidine-NH) or a bulky group or a

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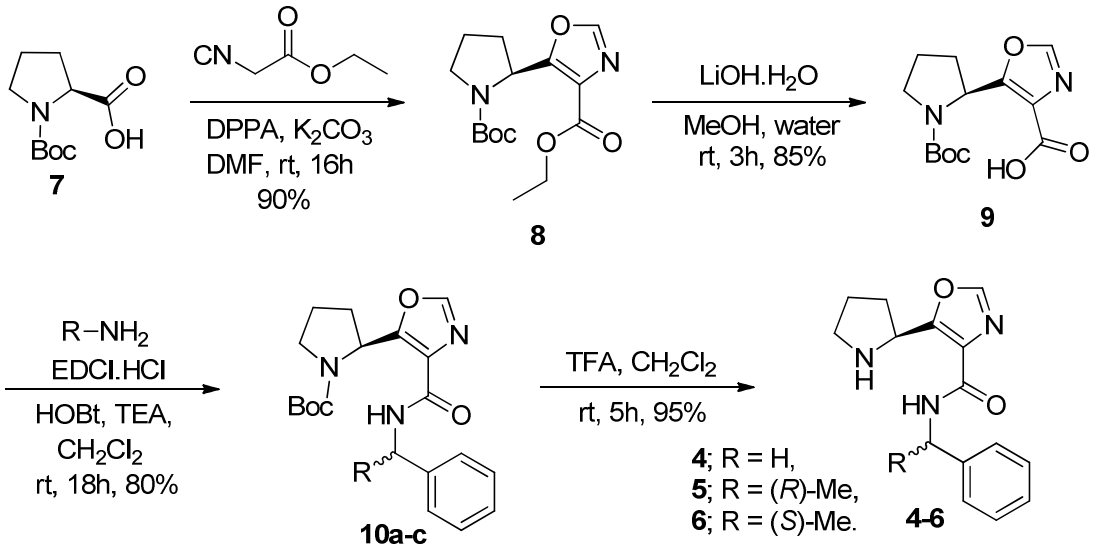
chiral template to form an efficient transition state.[23] In this context, we have fixed the hydrogen bond donating group at 6th position and introduced pyrrolidine-oxazole-carboxamides **4, 5** and **6**. These new catalysts were easily prepared in four steps from *N*-Boc-L-proline as shown in Scheme 1. By the modification of known procedures, the N-Boc-L-proline (**7**) was treated with ethyl isocyanoacetate and diphenylphosphoryl azide (DPPA) under basic condition to obtain the corresponding *N*-Boc-pyrrolidine-oxazole ester (**8**). Further, hydrolysis of ester **8** with aqueous lithium hydroxide affords **9**. Then this was coupled with three different benzyl amines followed by Boc-deprotection with TFA to provide the desired catalysts **4**, **5** and **6** in excellent yields.

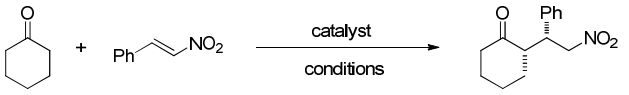


Scheme 1 Synthesis of pyrrolidinyl-oxazole-carboxamide derivatives **4**–**6**.

Initially, we attempted asymmetric Michael addition of cyclohexanone **11a** with *trans*-β-nitrostyrene **12a** by employing these organocatalysts **4**, **5** and **6**. Next, the catalysts **4**, **5** and **6** were screened from 10 mol % and tested down to 3 mol % in THF as solvent and *p*-nitro benzoic acid as an additive as shown in Table 1. It was observed that 5 mol % of the catalyst was adequate to achieve efficient yields with high enantioselectivity (entry 6, Table 1). It also indicates that the potential catalytic activity of these chiral ligands even utilized lower amount of catalyst loading. Catalyst **6** was found to be slightly superior to promote the asymmetric Michael addition reaction with higher diastereo enantioselectivity in comparison to **4** and **5** (entry 3 and 6, Table 1).

The effect of solvent in the asymmetric Michael addition was studied by using various solvents (Table 2). In protic solvents, such as MeOH, water and IPA, the Michael adducts were obtained in trace amounts (entry 6, 12 and 18, Table 2), whereas in toluene and chloroform, the adducts were formed in moderate yields and lower selectivity (entry 9 and 21, Table 2). Interestingly, it was found that higher yields and enantioselectivities were observed in case of a neat reaction (Table 2).

Table 1 Michael addition of *trans*-β-nitrostyrene to cyclohexanone by using catalysts **4**, **5** and **6**[a]



11a **12a** **13a**

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]	Dr (*syn/anti*)[c]	Ee (%)[d]
1	**4** (3)	THF	18	89	85:15	84
2	**5** (3)	THF	20	90	94:6	86
3	**6** (3)	THF	20	90	95:5	86
4	**4** (5)	THF	18	90	90:10	86
5	**5** (5)	THF	20	93	95:5	88
6	**6** (5)	THF	20	95	95:5	89

[a] Reactions were performed using **12a** (0.2 mmol), cyclohexanone (**11a**, 10 equiv.), 4-NBA (10 mol%) for given time. [b]Isolated yield. [c]The diastereomeric ratio (*dr*) was determined by ^{1}H NMR spectroscopy (400 MHz). [d]The enantiomeric excess (*ee*) was determined by chiral HPLC.

To examine the role of acid additives, initially the reaction was performed in the absence of additives, but the product was obtained in trace amounts (entry 30 and 31, Table 3). It indicates that an acid additive is required for the catalytic activity of

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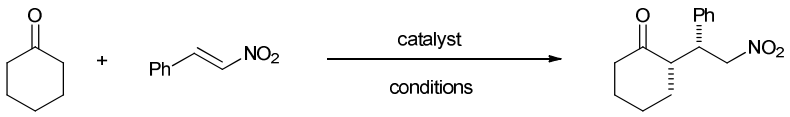
Michael addition. A considerable investigation of acid additives instead of *p*-nitrobenzoic acid, displayed the importance of the acidic counterpart (Table 3). Acid additive such as benzoic acid and trifluoroacetic acid did not work and gives only trace amount of the product (entries 10–15, 22 and 23, Table 3). Moreover, weak organic acids like citric acid contributed to moderate yield with poor selectivity (entries 16–21, Table 3). However, in case of acetic acid, the yields as well as selectivities were excellent. Considerably, high selectivities were observed under solvent-free reaction conditions compared to THF as a solvent (entries 24–26 *vs.* 27–29, Table 3).

Table 2 Solvent screening for the Michael addition of *trans*-β-nitrostyrene and cyclohexanone by using catalysts **4**, **5** and **6**[a]



11a **12a** **13a**

Entry	Catalyst (5 mol%)	Solvent	Time (h)	Yield (%)[b]	Dr (*syn/anti*)[c]	Ee (%)[d]
1	**4**	THF	18	99	> 99:1	94
2	**5**	THF	20	99	> 99:1	95
3	**6**	THF	20	99	> 99:1	95
4	**4**	MeOH	38	trace	-	-
5	**5**	MeOH	40	trace	-	-
6	**6**	MeOH	40	trace	-	-
7	**4**	toluene	36	45	-	55
8	**5**	toluene	40	50	-	59
9	**6**	toluene	40	50	-	60
10	**4**	water	48	trace	-	-
11	**5**	water	72	trace	-	-
12	**6**	water	72	trace	-	-
13	**4**	neat	18	99	> 99:1	95
14	**5**	neat	20	99	> 99:1	96
15	**6**	neat	20	99	> 99:1	98
16	**4**	IPA	36	trace	-	-
17	**5**	IPA	40	trace	-	-
18	**6**	IPA	40	trace	-	-
19	**4**	$CHCl_3$	24	60	-	53
20	**5**	$CHCl_3$	30	62	-	56
21	**6**	$CHCl_3$	30	65	-	58

[a]Reactions were performed using **12a** (0.2 mmol), cyclohexanone (**11a**, 10 equiv.), acetic acid (10 mol%) in 1 mL solvent for given time. [b]Isolated yield. [c]The diastereomeric ratio (*dr*) was determined by ^{1}H NMR spectroscopy (400 MHz). [d] The enantiomeric excess (*ee*) was determined by chiral HPLC.

With the optimized reaction conditions in hand, a series of nitroolefins with different substituents were investigated (Table 4). Various nitroolefins reacted evenly with cyclohexanone and observed the Michael adduct in good yields, excellent diastereo- and enantioselectivities (entries 1–21, Table 4). Typically, substituents on aryl ring slightly changed the diastereo- and enantioselectivities. For example, nitroolefins with aryl ring having electron-withdrawing group like $–CF_3$ gave the Michael adduct **13g** (entry 21, Table 4) with high selectivity (*dr* up to > 99:1 and *ee* 98%) in good yield (89%). Moreover, aryl rings having electron-donating groups like –Me, –OMe and halo group like –Cl gave the adducts **13b**, **13f** and **13e** with excellent yields and good selectivities (entries 6, 18 and 15, Table 4). Interestingly, the fused aromatic nitroolefin, such as **12d**, was successfully employed in this transformation and gave **13d** (entry 12, Table 4) with high yield (95%), *dr* (> 99:1) and *ee* (99%). Moreover, nitroolefin with the furan system was also provides the corresponding adduct **13c** (entry 9, Table 4) in high yields (94%), *dr* (> 99:1) and *ee* (94%).

The Michael reactions were examined with other ketones like tetrahydrothiopyran-4-one and tetrahydro-4*H*-pyran-4-one also suitable effective substrates as Michael donors and gave **13h** and **13i** (entries 22–27, Table 4) with considerable yields and selectivities. Moreover, this reaction with cyclopentanone produced the corresponding adduct **13j** (entry 28–30, Table 4) in good yields, with moderate selectivities.

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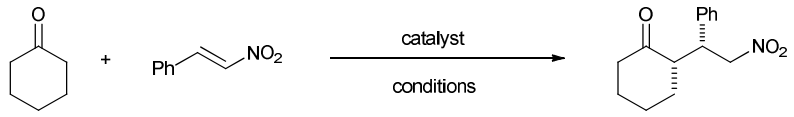
Table 3 Acid additives screening for the Michael addition of *trans*-β-nitrostyrene to cyclohexanone by using catalysts **4, 5** and **6**[a]



11a **12a** **13a**

Entry	Catalyst (5 mol%)	Additive (10 mol%)	Solvent	Time (h)	Yield (%)[b]	Dr (*syn/anti*)[c]	Ee (%)[d]
1	**4**[e]	4-NBA	THF	18	89	85:15	84
2	**5**[e]	4-NBA	THF	20	90	94:6	86
3	**6**[e]	4-NBA	THF	20	90	95:5	86
4	**4**	4-NBA	THF	18	90	90:10	86
5	**5**	4-NBA	THF	20	93	95:5	88
6	**6**	4-NBA	THF	20	95	95:5	89
7	**4**	4-NBA	neat	18	95	95:5	88
8	**5**	4-NBA	neat	20	98	97:3	90
9	**6**	4-NBA	neat	20	99	98:2	90
10	**4**	$PhCO_2H$	THF	36	trace	-	-
11	**5**	$PhCO_2H$	THF	40	trace	-	-
12	**6**	$PhCO_2H$	THF	40	trace	-	-
13	**4**	$PhCO_2H$	neat	36	trace	-	-
14	**5**	$PhCO_2H$	neat	40	trace	-	-
15	**6**	$PhCO_2H$	neat	40	trace	-	-
16	**4**	citric acid	THF	18	80	85:5	62
17	**5**	citric acid	THF	20	83	88:12	70
18	**6**	citric acid	THF	20	85	87:13	70
19	**4**	citric acid	neat	18	80	84:16	65
20	**5**	citric acid	neat	20	84	85:15	70
21	**6**	citric acid	neat	20	85	88:12	72
22	**6**	TFA	THF	40	trace	-	-
23	**6**	TFA	neat	40	trace	-	-
24	**4**	AcOH	THF	18	99	> 99:1	94
25	**5**	AcOH	THF	20	99	> 99:1	95
26	**6**	AcOH	THF	20	99	> 99:1	95
27	**4**	AcOH	neat	18	99	> 99:1	95
28	**5**	AcOH	neat	20	99	> 99:1	96
29	**6**	AcOH	neat	20	99	> 99:1	98
30	**6**	-	THF	30	trace	-	-
31	**6**	-	neat	30	trace	-	-

[a]Reactions were performed using **12a** (0.2 mmol), cyclohexanone **11a** (10 equiv.), acid additive (10 mol%) for given time. [b]Isolated yield. [c]The diastereomeric ratio (*dr*) was determined by ^{1}H NMR spectroscopy (400 MHz). [d]The enantiomeric excess (*ee*) was determined by chiral HPLC. [e]3 mol % of catalyst was used.

Further investigation with acetone (**14**) provided the desired product **15a** in 90% yield but with only 32% *ee* (entries 1–3, Table 5). However, the Michael additions of **14** with various substituted nitroolefins afforded adducts in excellent yields (up to 85–99%), but with very poor enantioselectivities (Table 5). Surprisingly, the fused aromatic nitroolefin **12d** gave the corresponding adduct **15d** in high yield (95%) and good selectivity (*ee* 96%, entry 6, Table 5).

A possible transition-state model was proposed to explain the stereochemical outcome of the asymmetric Michael addition reaction (Figure 2). Briefly in this proposed mechanism, ketones are activated by the secondary amine of the pyrrolidine ring of the catalyst through the formation of an enamine intermediate. The approach of the electrophile (nitroolefin) is controlled by the amide functional group through stabilizing interactions of hydrogen-bonding. The observed high enantio control can be accounted to hypothesize the stabilized interactions of the amide functional group with the nitroolefin which controls the face of the nucleophilic attack. However, the approach of electrophile is irrespective of the configuration of the stereogenic center of the *N*-benzyloxazole-carboxamide system (entry 2 and 3, Table 4).

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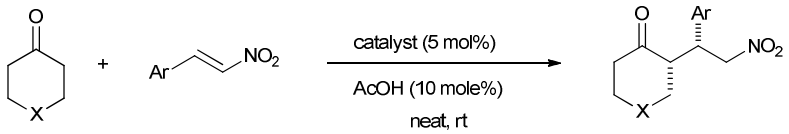
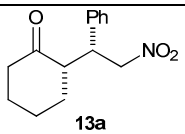
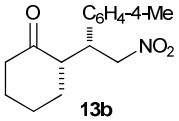
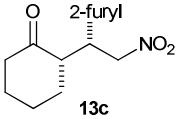
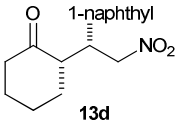
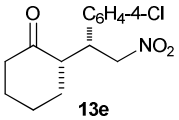
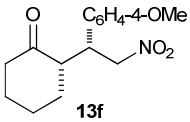
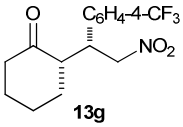
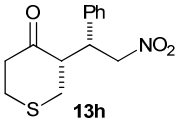
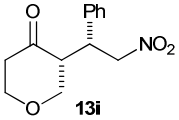
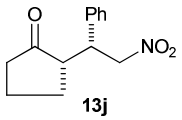
Table 4 Michael addition of *trans*-β-nitrostyrene and cyclic ketones by using catalysts **4, 5** and **6**[a]



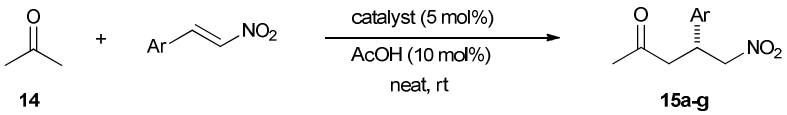
13a-j

Entry	Product	Catalyst (5 mol%)	Time (h)	Yield (%)[b]	Dr (*syn/anti*)[c]	Ee (%)[d]
1	 **13a**	**4**	18	99	> 99:1	96
2		**5**	20	99	> 99:1	98
3		**6**	20	99	> 99:1	98
4	 **13b**	**4**	18	96	> 99:1	92
5		**5**	24	95	> 99:1	93
6		**6**	24	97	> 99:1	96
7	 **13c**	**4**	18	92	97:3	92
8		**5**	20	90	98:2	94
9		**6**	20	94	> 99:1	94
10	 **13d**	**4**	18	89	97:3	96
11		**5**	24	93	> 99:1	97
12		**6**	24	95	> 99:1	99
13	 **13e**	**4**	18	89	> 99:1	90
14		**5**	22	90	> 99:1	91
15		**6**	22	92	> 99:1	92
16	 **13f**	**4**	18	85	95:5	95
17		**5**	20	89	98:2	95
18		**6**	20	90	98:2	92
19	 **13g**	**4**	18	85	96:4	97
20		**5**	24	86	97:3	96
21		**6**	24	89	98:2	98
22[e]	 **13h**	**4**	24	85	95:5	82
23[e]		**5**	30	90	97:3	82
24[e]		**6**	30	92	97:3	94
25	 **13i**	**4**	24	90	> 99:1	90
26		**5**	30	92	> 99:1	91
27		**6**	30	95	> 99:1	92

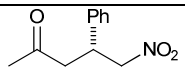
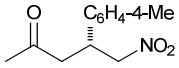
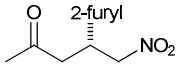
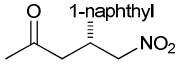
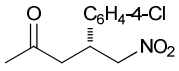
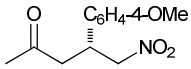
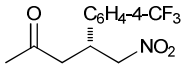
28		**4**	36	55	85:15	80
29		**5**	40	60	90:10	86
30		**6**	40	65	90:10	86 (44% *ee anti*)
	13j					

[a]Reactions were performed using nitroolefins **12a–g** (0.2 mmol), ketone (**11a–d**, 10 equiv.), acetic acid (10 mol%) for given time. [b]Isolated yield. [c]The diastereomeric ratio (*dr*) was determined by ^{1}H NMR spectroscopy (400 MHz). [d]The enantiomeric excess (*ee*) was determined by chiral HPLC. [e]1 ml THF was used as solvent.

Table 5 Michael addition of *trans*-β-nitrostyrene and acetone by using catalysts **4, 5** and **6**[a]



14 **15a-g**

Entry	Product	Catalyst (5 mol%)	Ee (%)[b]
1		4	30
2		5	32
3	**15a**	6	32
4	 **15b**	6	18
5	 **15c**	6	6
6	 **15d**	6	96
7	 **15e**	6	28
8	 **15f**	6	22
9	 **15g**	6	26

[a]Reactions were performed by using catalyst **6** (5 mol%), 0.2 mmol **12**, acetone (**14**, 10 equiv.) and acetic acid (10 mol%). [b]The enantiomeric excess (*ee*) was determined by chiral HPLC.

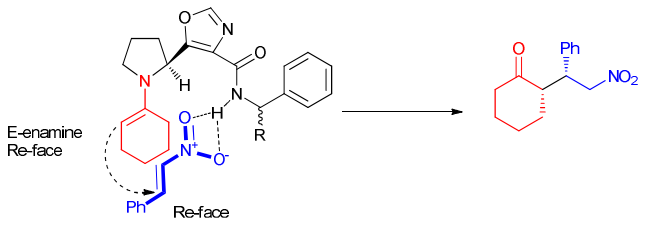


Fig. 2 Proposed transition state for the asymmetric Michael addition by employing catalysts **4**–**6**.

Computational mechanistic study

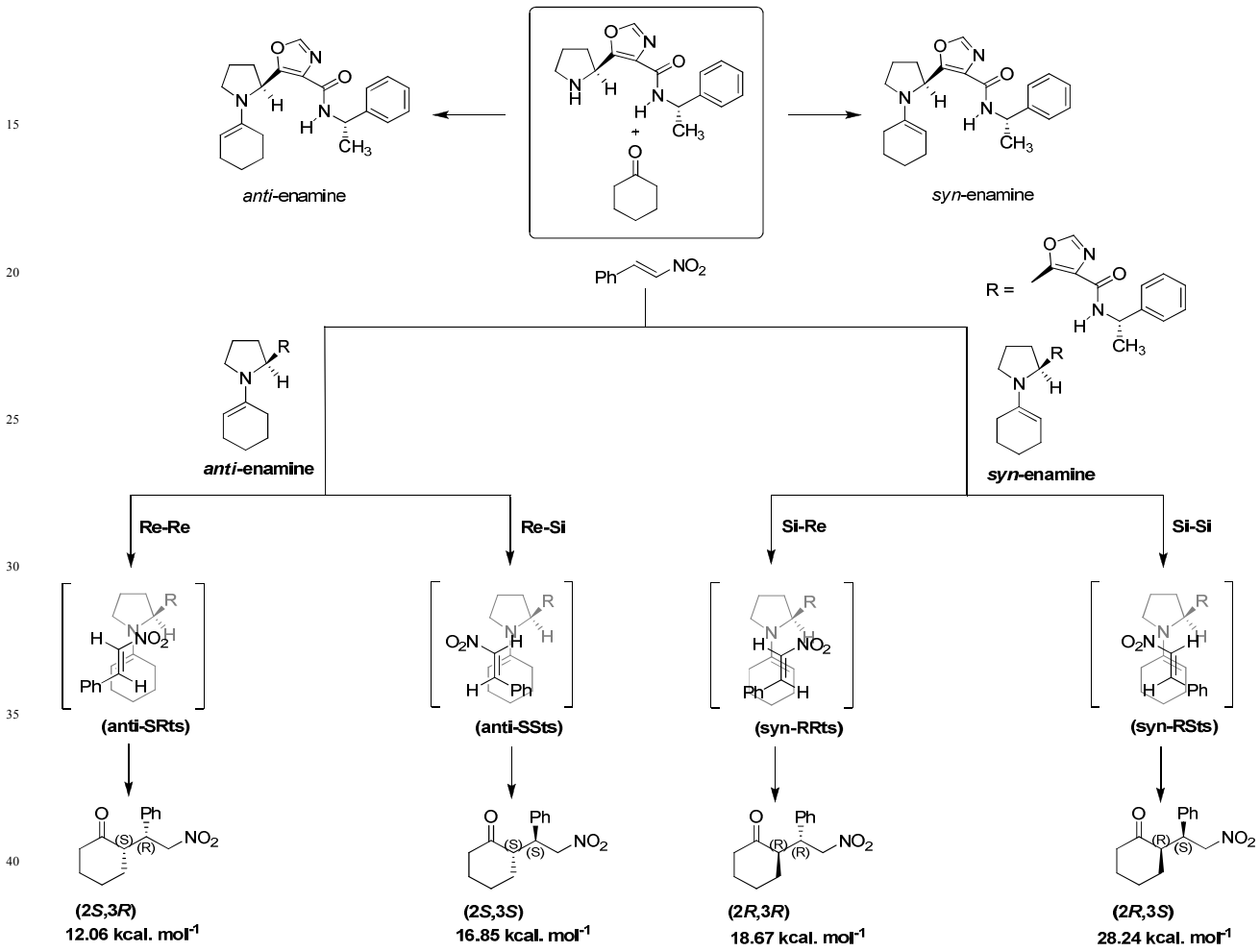


Fig. 3 Proposed intermediates and the corresponding activation energies for the Michael addition of cyclohexanone to *trans*-β-nitrostyrene catalyzed by **6**.

Density functional theory calculations at the B3LYP/6-31G* level in gas phase have been carried out in the Gaussian 03 software package to gain a more detailed understanding of the observed stereoselectivity in the Michael addition of cyclohexanone with trans-β-nitrostyrene catalyzed by **6**. We have assumed that the rate-limiting step involves the formation of C–C bond between nucleophilic enamine intermediate and activated trans-β-nitrostyrene, since the formation of the enamine and the final hydrolysis of the Michael addition adduct are fast and have no effect on the rate and stereoselectivity of the reaction.

The enamine intermediates can adopt *anti* and *syn* conformations and their C–C bond addition with trans-β-nitrostyrene are of four ways as indicated by *Re-Re, Re-Si, Si-Re,* and *Si-Si* in Figure 3. These additions lead to 2*S*, 3*R*; 2*S*, 3*S*; 2*R*, 3*R* and 2*R*, 3*S* stereoisomers of the Michael adducts respectively. The stereochemistry of the overall process is determined by the addition of *trans*-β-nitrostyrene to the *re*-face or *si*-face of enamine intermediate. The activation energies for the different transition states are given in Figure 3.

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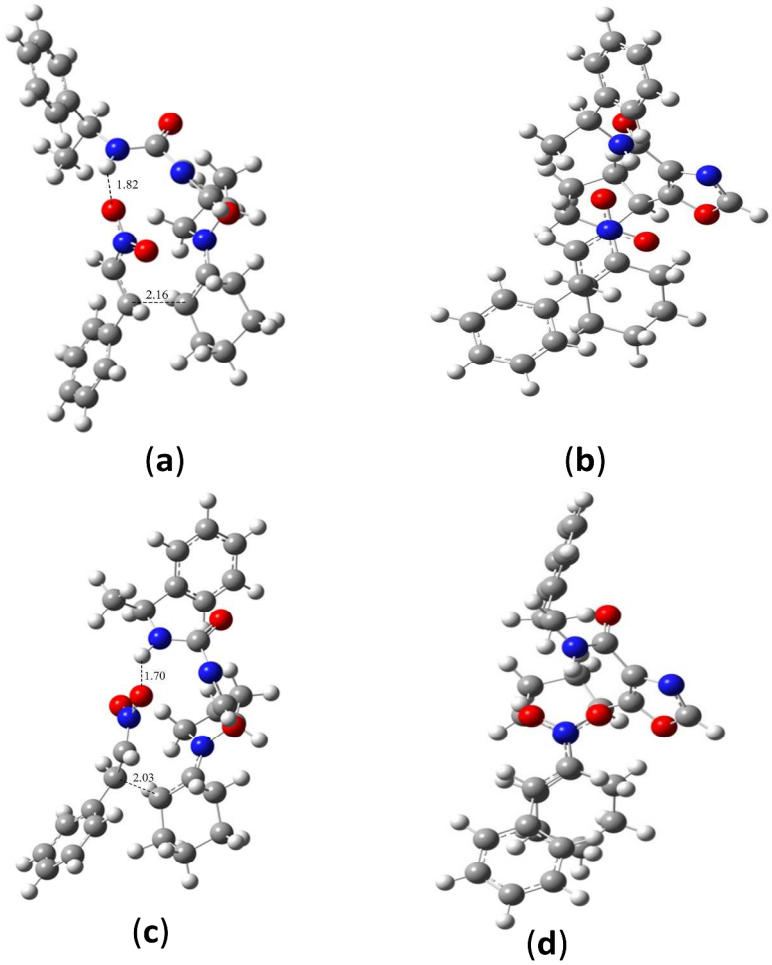

Fig. 4 The calculated transition structures of (**anti-SRts**) showing staggered forming C–C bond (**a,b**) and (**anti-SSts)** showing eclipsed C–C forming bond (**c,d**).

Also, the reactions involving *anti*-enamine were found to be exothermic whereas, those involving the *syn*-enamine were endothermic which meant the products from *syn*-enamine were energy-unfavorable. Among the transition states, those corresponding to the *re*-face attack on the anti-enamine leading to 2*S*, 3*R*-isomer (*anti*-SRts) were lower in energy than that involving *si* attack for 2*S*, 3*S* isomer (*anti*-SSts) by 4.79 kcal mol^{-1}, thus being in good agreement with the experimental results where 2*S*, 3*R* isomer (*syn*-diastereomer) is the major product.

We found that intermolecular H-bonds and the steric hindrance of the *N*-benzyloxazole-carboxamide moiety on the *si*-face of enamine dominate the stereoselectivity and catalytic activity. Due to the hydrogen bond formation between the amide proton in the enamine and nitro group of trans-β-nitrostyrene (CON-H···O-N=O), enamine could act as a nucleophile and attacks the nitroolefin from either the *re*-face or *si*-face.

In contrast to the *si*-facial attack, *re*-facial approach is less sterically demanding, because a lower steric repulsion between the phenyl group and enamine in the staggered conformation of the transition state during the formation of new C–C bond. Among all the four possible transition states, *anti*-SRts is the most stabilized transition state with activation energy of 12.06 kcal mol^{-1} and it yields the corresponding 2S, 3R-isomer as the major product in this asymmetric catalytic reaction. The other transition state in the re-facial attack (*anti*-SSts) was less stable due to the eclipsed arrangement of phenyl group and enamine in the transition state of the newly forming C–C bond. However, the presence of strongest hydrogen bond (1.70Å) in *anti*-SSts offers

enough stabilization for the formation of the corresponding 2S, 3S-isomer in minor quantities. In the case of *syn*-enamines, activation energy of both the transition states (*syn*-RRts and *syn*-RSts) were quite high (18.67kcal mol^{-1} and 28.24 $kcalmol^{-1}$) due to the steric hindrance of phenyl group.

The imaginary frequency obtained from vibrational frequency calculations mainly involves the motion of the formation of a C–C bond between the enamine and trans-β-nitrostyrene. Hence, the computational results are in good agreement with the experimental observations and reveals a valuable clue for the further catalyst design with high catalytic efficiency.

Conclusion

In conclusion, we have rationally designed and developed pyrrolidinyl-oxazole-carboxamides as new chiral bifunctional organocatalysts, useful in the asymmetric Michael addition of ketones with nitroolefin. These chiral catalysts were easily prepared from commercially available *N*-Boc-L-proline and are highly efficient in catalyzing the Michael reaction by offering excellent enantio- as well as diastereoselectivities in high yields. Moreover, all the reactions were performed in solvent free conditions. In addition, computational mechanistic studies were also performed that are in agreement with the experimental observations, thereby providing some useful inputs for the design of newer catalysts with improved catalytic efficiency. Further investigations in the wide application of such chiral catalysts for related asymmetric reactions are currently in progress and will be reported in due cource.

Experimental section

Physical measurements and materials

Chemical reagents were purchased from Sigma–Aldrich and used without further purification. All the solvents were commercial grade and purified prior to use when necessary. ^{1}H NMR and ^{13}C NMR experiments were performed at Avance (400 MHz) spectrometre. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 ($CDCl_3$) and are reported in parts per million (ppm). Spin multiplicities are described as s (singlet), br (broad singlet), d (doublet), dd (double doublet), t (triplet), td (triple doublet), q (quartet), or m (multiplet). Coupling constants are reported in Hertz (Hz). TLC analyses were performed with silica gel plates (0.25 mm, E. Merck, 60 F254) using iodine, $KMnO_4$, and a UV lamp for visualization. Specific rotations were measured on a Perkin-Elmer 341MC polarimeter. Enantiomeric excesses were determined on a HP-1100 instrument (chiral column; mobile phase: hexane/*i*-PrOH). Mass spectra were recorded by electrospray ionization mass spectrometry (ESIMS). HRMS was performed on a Varian QFT-ESI instrument. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. IR spectra were measured on Bruker FT-IR Equinox 55 and Bruker TENSOR 27 instruments.

Computational methods

All the calculations were carried out using the Gaussian 03 suite of programs. All the geometries were fully optimized using DFT approaches at the B3LYP/6-31G* level in gas phase followed by harmonic vibrational frequency calculations to determine the nature (local minima or first-order saddle points) of the stationary points. The transition state was verified by the existence of an imaginary frequency. The energies reported include the zero-point energy corrections. The intrinsic reaction coordinate (IRC) calculations were performed to confirm the connectivity between the saddle points and minima.

(*S*)-Ethyl 5-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)oxazole-4-carboxylate (8)

To a stirred solution of *N*-boc-L-proline (**7**, 215 mg, 1mmol) in Dry DMF (20 mL) was added K_2CO_3 (345 mg, 2.5 mmol) and diphenylphosphoryl azide (238 µL, 1.1 mmol). The reaction mixture was stirred at room temperature for 5 min and added ethyl isocyanoacetate (120 µL, 1.1 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 16 h. After removal of solvent, the residue was taken into ethyl acetate (60 mL) and washed with ice cold water (2x30 mL) and the organic phase was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (ethyl acetate/hexane = 1:4) and fractions were collected and concentrated *in vacuo* to afford compound **8** as thick syrup (279 mg, 90%). $[\alpha]_D^{25}$ = +16.6 (*c* = 0.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (s, 1H), 5.60–5.52 (m, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 3.65–3.55 (m, 2H), 2.42–2.34 (m, 1H), 2.11–2.03 (m, 1H), 2.01–1.92 (m, 2H), 1.44 and 1.25 (2xs, 9H), 1.40 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.6, 160.2, 153.7, 148.7, 126.7, 79.8, 61.1, 52.5 (52.9), 46.6 (46.9), 32.6 (32.3), 28.4, 28.0, 23.8 (24.4), 14.3 ppm; IR (KBr): 3123.49, 2976.59, 1737.97, 1698.42, 1393.10 cm^{-1}; MS (ESI): *m/z* 333 (M + Na)$^+$; HRMS calculated for $C_{15}H_{22}N_2NaO_5$ *m/z* 333.14222, found *m/z* 333.14217.

(*S*)-5-(1-(tert-Butoxycarbonyl)pyrrolidin-2-yl)oxazole-4-carboxylic acid (9)

To a stirred mixture of compound **8** (310 mg, 1 mmol) in methanol (20 mL) was added aqueous solution of lithium hydroxide monohydrate (84 mg, 2 mmol in 20 mL water) at 0 °C and stirred for 3 h. The methanol was evaporated *in vacuo* and the basic aqueous phase was washed with ethyl acetate (2x20 mL). The aqueous phase was acidified with saturated citric acid solution and extracted with chloroform (2x30 mL). The combined extracts were washed with brine (30 mL), then dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to get crude product which was crystallized in 20% ethyl acetate and n–hexane to afford 238 mg (85%) of corresponding acid **9** as white solid, mp: 152–155 °C; $[\alpha]_D^{25}$ = +10.1 (*c* = 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (s, 1H), 5.59–5.38 (m, 1H), 3.66–3.45 (m, 2H), 2.44–2.30 (m, 1H), 2.22–1.94 (m, 3H), 1.44 and 1.26 (2xs, 9H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ: 161.2, 153.8, 149.0, 129.6, 127.9, 80.1 (81.0), 52.5 (52.4), 46.6 (49.9), 32.7 (31.6), 28.0 (28.3), 23.9 (24.5) ppm; IR (KBr): 3439.93, 3124.51, 2974.51, 1737.61, 1696.48, 1393.69 cm^{-1}; MS (ESI): *m/z* 283 (M + H)$^+$; HRMS calculated for $C_{13}H_{18}N_2NaO_5$ *m/z* 305.11088, found *m/z* 305.11069.

General procedure for the synthesis of compounds (10a-c)

The acid compound **9** (1 mmol) was taken into dichloromethane (20 mL) and cooled to 0 °C. Then added EDC.HCl (1.2 mmol), HOBt (1.2 mmol) and triethylamine (3 mmol). The reaction mixture was stirred for 15 min and then added required

benzylamine (1.1 mmol) and stirred for 18 h. The reaction mixture was diluted with dichlomethane (20 mL) and washed with water (30 mL), brine (30 mL), then the organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford crude product. The crude product was purified by silica gel chromatography (ethyl acetate/hexane = 3:10) and fractions were collected and concentrated *in vacuo* to afford **10a–c.**

(*S*)-*tert*-Butyl 2-(4-(benzylcarbamoyl)oxazol-5-yl)pyrrolidine-1-carboxylate (10a). Light brown solid: yield 80%; mp: 110–115 ^{o}C; $[a]_D^{25}$ = +3.0 (*c* = 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (s, 1H), 7.54 (s, br, 1H), 7.36–7.24 (m, 5H), 5.70, 5.59 (2xm, 1H), 4.58 (qd, *J* = 6.1, 14.5, 20.5 Hz, 2H), 3.59, 3.49 (2xm, 2H), 2.43–2.32 (m, 1H), 2.08–1.90 (m, 3H), 1.64, 1.42 and 1.23 (3xs, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.8, 159.9, 157.2, 148.0, 147.8, 138.0, 128.6, 127.8, 127.4, 79.6 (79.7), 52.4 (52.6), 46.6 (46.9), 42.8 (43.0), 32.7 (32.2), 28.0 (28.3), 23.9 ppm; IR (KBr): 3346.26, 3112.09, 2981.40, 1689.15, 1650.03, 1620.19, 1521.64, 1406.44; MS (ESI): *m/z* 372 $(M + H)^+$; HRMS calculated for $C_{20}H_{26}N_3O_4$ *m/z* 372.19258, found *m/z* 372.19267.

(*S*)-*tert*-Butyl 2-(4-(((*R*)-1-phenylethyl)carbamoyl)oxazol-5-yl)pyrrolidine-1-carboxylate (10b). Light brown solid: yield 80%; mp: 160–170 ^{o}C; $[a]_D^{25}$ = +62.8 (*c* = 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (s, 1H), 7.41–7.17 (m, 6H), 5.71–5.64 (m, 1H), 5.29–5.20 (m, 1H), 3.61–3.53 (m, 2H), 2.40–2.31 (m, 1H), 2.07–1.87 (m, 3H), 1.56 (d, *J* = 6.9 Hz, 3H), 1.43, 1.27 and 1.13 (3xs, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.0, 157.2, 153.9, 147.8, 143.2, 128.6, 127.2, 126.3, 126.1, 79.5, 52.3, 48.4, 46.6, 32.7 (32.2), 28.4, 28.1, 27.9 (24.4), 23.8, 22.0 ppm; IR (KBr): 3355.70, 3117.82, 2981.14, 2891.49, 1685.10, 1648.57, 1525.84, 1455.97 cm^{-1}; MS (ESI): *m/z* 386 $(M+H)^+$; HRMS calculated for $C_{21}H_{28}N_3O_4$ *m/z* 386.20798, found *m/z* 386.20839.

(*S*)-*tert*-Butyl 2-(4-(((*S*)-1-phenylethyl)carbamoyl)oxazol-5-yl)pyrrolidine-1-carboxylate (10c). White solid: yield 80%; mp: 165–175 ^{o}C; $[a]_D^{25}$ = –48.8 (*c* = 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (s, 1H), 7.39–7.19 (m, 6H), 5.70–5.62 (m, 1H), 5.29–5.18 (m, 1H), 3.62–3.53 (m, 2H), 2.42–2.30 (m, 1H), 2.07–1.87 (m, 3H), 1.58 (d, *J* = 7.7 Hz, 3H), 1.43, 1.27 and 1.13 (3xs, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.0, 157.2, 153.9, 147.8, 143.2, 128.6, 127.2, 126.3, 126.1, 79.5, 52.3, 48.4, 46.6, 32.7 (32.2), 28.4, 28.1, 27.9 (24.4), 23.8, 22.0; IR (KBr): 3355.31, 3118.74, 2980.21, 2889.69, 1690.57, 1649.08, 1523.95, 1477.68 cm^{-1}; MS (ESI): *m/z* 386 $(M+H)^+$; HRMS calculated for $C_{21}H_{28}N_3O_4$ *m/z* 386.20855, found *m/z* 386.20861.

General procedure for the preparation of compounds (4-6).

The *N*-Boc-derivative **10a–c** (1.0 mmol) was dissolved in dichloromethane (20 mL) and added trifluoroacetic acid (1.5 mL) at 0 ^{o}C. The resulting mixture was stirred at room temperature for 5 h. After removal of solvent, the residue was taken into water (30 mL) and washed with diethyl ether (2x20 mL). Then the acidic phase was basified by adding 10% Na_2HCO_3 solution and extracted with $CHCl_3$ (3x20 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), the organic phase was dried over Na_2SO_4 and concentrated *in vacuo* after filtration to get crude products which were purified by crystallization in 20% ethyl acetate and hexane to afford **5a-c**.

(*S*)-*N*-Benzyl-5-(pyrrolidin-2-yl)oxazole-4-carboxamide (4). Light yellow solid: yield 80%; mp: 85–90 ^{o}C; $[a]_D^{25}$ = –2.2 (*c* = 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (s, 1H), 7.55 (s, br, 1H), 7.36–7.27 (m, 5H), 4.97 (t, *J* = 7.4 Hz, 1H), 4.59 (d, *J* = 6.0 Hz, 2H), 3.19–3.11 (m, 1H), 3.08–3.00 (m, 1H), 2.24–2.14 (m, 1H), 2.02–1.85 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.2, 157.1, 148.2, 137.8, 128.9, 128.6, 127.7, 127.4, 53.2, 46.7, 42.9, 30.7, 25.5 ppm; IR (KBr): 3323.79, 3140.44, 3026.21, 2973.32, 2925.54, 2870.40, 654.12, 1605.42, 1521.79, 1452.79 cm^{-1}; MS (ESI): *m/z* 272 $(M+H)^+$; HRMS calculated for $C_{15}H_{18}N_3O_2$ *m/z* 272.13975, found *m/z* 272.13982.

***N*-((*R*)-1-Phenylethyl)-5-((*S*)-pyrrolidin-2-yl)oxazole-4-carboxamide (5).** Light yellow solid: yield 80%; mp: 100–105 ^{o}C; $[a]_D^{25}$ = +88.6 (*c* = 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (s, 1H), 7.44 (d, br, *J* = 6.7 Hz, 1H), 7.38–7.25 (m, 5H), 5.23 (m, 1H), 4.93 (t, *J* = 7.3 Hz, 1H), 3.17–3.11 (m, 1H), 3.05–2.99 (m, 1H), 2.26–2.13 (m, 2H), 1.99–1.83 (m, 3H), 1.58 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.5, 156.4, 148.3, 129.0, 128.7, 127.3, 126.0, 53.1, 48.5, 46.5, 30.8, 25.2, 21.9, 21.8 ppm; IR (KBr): 3405.04, 3274.95, 2969.07, 1649.24, 1610.03, 1523.11, 1449.56 cm^{-1}; MS (ESI): *m/z* 286 $(M+H)^+$; HRMS calculated for $C_{16}H_{20}N_3O_2$ *m/z* 286.15532, found *m/z* 286.15537.

***N*-((*S*)-1-Phenylethyl)-5-((*S*)-pyrrolidin-2-yl)oxazole-4-carboxamide (6).** Light yellow solid: yield 80%; mp: 98–104 ^{o}C; $[a]_D^{25}$ = –462.3 (*c* = 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (s, 1H), 7.46 (d, br, *J* = 7.0 Hz, 1H), 7.38–7.25 (m, 5H), 5.23 (m, 1H), 4.96 (t, *J* = 7.3 Hz, 1H), 3.19–3.13 (m, 1H), 3.10–3.00 (m, 2H), 2.25–2.16 (m, 1H), 2.01–1.86 (m, 3H), 1.58 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.5, 156.4, 148.3, 129.0, 128.7, 127.3, 126.0, 53.1, 48.5, 46.5, 30.8, 25.2, 21.9, 21.8 ppm; IR (KBr): 3405.10, 3274.68, 2968.92, 1649.28, 1609.96, 1523.03, 1449.43 cm^{-1}; MS (ESI): *m/z* 388 $(M+H)^+$; HRMS calculated for $C_{16}H_{20}N_3O_2$ *m/z* 286.15551, found *m/z* 286.15553.

General procedure for the Michael reaction of cyclohexanones with nitrostyrenes

A mixture of the catalyst **6** (0.01 mmol), acetic acid (0.02 mmol) in cyclohexanone (2 mmol) was stirred at room temperature for 5 min. To the resulting mixture was added nitroolefin (0.2 mmol) at the room temperature. After the reaction was complete (monitored by TLC), the excess cyclohexanone was removed on reduced pressure and purified by column chromatography on silica gel (200–300 mesh, hexane/ethyl acetate = 15:1–10:1) to afford the product.

(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclohexanone (13a)[21,26]. White solid: yield 99%; *syn*/*anti* = > 99/1, 98% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.23 (m, 3H), 7.18–7.15 (m, 2H), 4.94 (dd, *J* = 4.5, 12.5 Hz, 1H), 4.64 (dd, *J* = 9.8, 12.5 Hz, 1H), 3.76 (td, *J* = 4.5, 9.8 Hz, 1H) 2.74–2.64 (m, 1H), 2.52–2.43 (m, 1H), 2.42–2.33 (m, 1H), 2.13–2.05 (m, 1H), 1.83–1.65 (m, 3H), 1.62–1.50 (m, 1H), 1.30–1.17 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.9, 137.8, 128.8, 128.1, 127.7, 78.8, 52.48, 43.8, 42.7, 303.2, 28.5, 25.0 ppm; Chiral HPLC analysis: Chiralpak AS-H column, hexane/2-propanol = 95/5, flow rate: 1.0 mL/min, λ = 210 nm, *R*t = 12.45 min (*minor*) and 16.46 min (*major*).

(*S*)-2-((*R*)-2-Nitro-1-(*p*-tolyl)ethyl)cyclohexanone (13b)[27]. White solid: yield 97%; *syn*/*anti* = > 99/1, 96% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.12 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 4.92 (dd, *J* = 4.4, 12.4 Hz, 1H), 4.61 (dd, *J* = 9.9, 12.4 Hz,

1H), 3.72 (td, *J* = 4.6, 9.9 Hz, 1H), 2.70–2.64 (m, 1H), 2.50–2.45 (m, 1H), 2.42–2.34 (m, 1H), 2.31 (s, 3H), 211–2.04 (m, 1H), 1.81–1.64 (m, 3H), 1.61–1.52 (m, 1H), 1.27–1.19 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.0, 137.4, 134.5, 129.6, 128.0, 79.0, 52.6, 43.5, 42.7, 33.1, 28.5, 25.0, 21.0 ppm; Chiral HPLC analysis: Chiralpak AD-H column, hexane/2-propanol = 95/5, flow rate = 1.0 mL/min; λ = 210 nm, *R*t = 8.11 min (*minor*) and 9.93 min (*major*).

(*S*)-2-((*S*)-1-(Furan-2-yl)-2-nitroethyl)cyclohexanone (13c)[28]. Brown oil: yield 94%; *syn*/*anti* = > 99/1, 94% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (s, 1H), 6.30–6.27 (m, 1H), 6.20–6.17 (m, 1H), 4.79 (dd, *J* = 5.3, 12.8 Hz, 1H), 4.67 (dd, *J* = 9.0, 12.8 Hz, 1H), 3.97 (td, *J* = 4.5, 9.0 Hz, 1H), 2.80–2.70 (m, 1H), 2.50–2.30 (m, 2H), 2.15–2.04 (m, 1H), 1.88–1.57 (m, 4H), 1.36–1.21 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.9, 150.8, 142.3, 110.2, 108.9, 76.5, 51.0, 42.5, 37.5, 32.4, 28.1, 25.0 ppm; Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 1 mL/min; λ = 210 nm, *R*t = 12.52 min (*major*) and 15.00 (*minor*).

(*S*)-2-((*R*)-1-(Naphthalen-1-yl)-2-nitroethyl)cyclohexanone (13d)[28*b*,29]. Light brown solid: yield 95%; *syn*/*ant* = > 99/1, 99% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (s, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.60–7.35 (m, 4H), 5.07 (dd, *J* = 4.5, 12.8 Hz, 1H), 4.91 (dd, *J* = 9.8, 12.8 Hz, 1H), 4.76 (s, 1H), 2.87 (m, 1H), 2.55–2.36 (m, 2H), 2.13–2.04 (m, 1H), 1.73–1.49 (m, 4H), 1.33–1.19 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.3, 134.5, 133.9, 132.2, 128.9, 128.1, 126.5, 125.8, 125.3, 123.5, 122.7, 78.6, 53.7, 42.8, 36.7, 33.2, 28.6, 25.2 ppm; Chiral HPLC analysis: Chiralpak AD-H column, hexane/2-propanol = 95/5, flow rate = 1.0 mL/min; λ = 220 nm, *R*t = 13.75 min (*minor*) and 18.65 min (*major*).

(*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone (13e)[30]. White solid: yield 92%; *syn*/*anti* = > 99/1, 92% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 4.94 (dd, *J* = 4.5, 12.6 Hz, 1H), 4.60 (dd, *J* = 10.2, 12.6 Hz, 1H), 3.76 (td, 4.5, 10.0 Hz, 1H), 2.70–2.60 (m, 1H), 2.52–2.32 (m, 2H), 2.15–2.05 (m, 1H), 1.85–1.50 (m, 4H), 1.30–1.16 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.4, 136.3, 133.6, 129.5, 129.1, 78.6, 52.4, 43.4, 42.7, 33.1, 28.4, 25.0 ppm; Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 1 mL/min; λ = 254 nm, *R*t = 14.57 min (*minor*) and 17.55 min (*major*).

(*S*)-2-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (13f)[29,21]. White solid: yield 90%; *syn*/*anti* = 98/2, 92% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.08 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.91 (dd, *J* = 4.6, 12.2 Hz, 1H), 4.58 (dd, *J* = 10.1, 12.4 Hz, 1H), 3.78 (s, 3H), 3.71 (td, *J* = 4.6, 9.9 Hz, 1H), 2.68–2.62 (m, 1H), 2.50–2.45 (m, 1H), 2.42–2.35 (m, 1H), 2.11–2.04 (m, 1H), 1.82–1.63 (m, 3H), 1.62–1.53 (m, 1H), 1.27–1.19 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.0, 158.9, 129.5, 129.1, 114.2, 79.1, 55.1, 52.6, 43.1, 42.6, 33.1, 28.4, 24.9 ppm; Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 1 mL/min; λ = 210 nm, *R*t = 11.20 min (*minor*) and 13.43 min (*major*).

(*S*)-2-((*R*)-2-Nitro-1-(4-(trifluoromethyl)phenyl)ethyl)cyclohexanone (13g)[31]. White solid: yield 89%; *syn*/*anti* = 98/2, 98% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 7.5 Hz, 2H), 4.98 (dd, *J* = 4.5, 12.8 Hz, 1H), 4.67 (dd, *J* = 9.8, 12.8 Hz, 1H), 3.86 (td, *J* = 4.5, 9.8 Hz, 1H), 2.75–2.65 (m, 1H), 2.53–2.33 (m, 2H), 2.15–2.07 (m, 1H), 1.86–1.77 (m, 1H), 1.76–1.52 (m, 3H), 1.31–1.17 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.1, 142.0, 136.2, 129.9, 128.6, 125.9 (q, *J* = 3.8 Hz), 78.2, 52.3, 43.7, 42.7, 33.2, 28.4, 25.1 ppm; Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 1 mL/min; λ = 210 nm, *R*t = 11.33 min (*minor*) and 13.80 min (*major*).

(*S*)-3-((*R*)-2-Nitro-1-phenylethyl)dihydro-2*H*-thiopyran-4(3*H*)-one (13h)[27,31]. White solid: yield 92%; *syn*/*anti* = 97/3, 94% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.29 (m, 3H), 7.23–7.17 (m, 2H), 4.74 (dd, *J* = 4.5, 12.6 Hz, 1H), 4.63 (dd, *J* = 9.6, 12.6 Hz, 1H), 3.98 (td, *J* = 4.5, 10.4 Hz, 1H), 3.10–2.92 (m, 3H), 2.90–2.75 (m, 2H), 2.66–2.58 (m, 1H), 2.50–2.41 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.5, 136.4, 129.3, 128.3, 128.1, 78.6, 55.0, 44.5, 43.5, 35.1, 31.6 ppm; Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 85/15, flow rate 1 mL/min; λ = 254 nm, *R*t = 12.24 min (*minor*) and 22.15 min (*major*).

(*R*)-3-((*R*)-2-Nitro-1-phenylethyl)dihydro-2*H*-pyran-4(3*H*)-one (13i)[27,31]. Light yellow solid: yield 95%; *syn*/*anti* = > 99/1, 92% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38–7.28 (m, 3H), 7.21–7.17 (m, 2H), 4.94 (dd, *J* = 4.5, 12.8 Hz, 1H), 4.65 (dd, *J* = 10.6, 12.8 Hz, 1H), 4.19–4.11 (m, 1H), 3.88–3.76 (m, 2H), 3.75–3.66 (m, 1H), 3.27 (dd, *J* = 9.1, 12.1 Hz, 1H), 2.93–2.84 (m, 1H), 2.71–2.63 (m, 1H), 2.60–2.53 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.4, 136.1, 129.2, 128.3, 127.8, 78.6, 71.5, 68.9, 53.2, 42.9, 41.2 ppm; Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 85/15, flow rate 1 mL/min, λ = 210 nm, *R*t = 10.99 min (*minor*) and 16.01 min (*major*).

(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclopentanone (13j)[31]. Light brown liquid: yield 65%; *syn*/*anti* = 90/10, *syn* = 86% *ee* and *anti* = 44% *ee*; ^{1}H NMR (400 MHz, CDCl3) δ: 7.36–7.24 (m, 3H), 7.20–7.13 (m, 2H), 5.34 (dd, *J* = 5.7, 12.8 Hz, 0.9H), 5.02 (d, *J* = 7.7 Hz, 0.2H), 4.71 (dd, *J* = 10.0, 12.8 Hz, 0.9H), 3.83 (td, *J* = 3.9, 7.5 Hz, 0.1H), 3.69 (td, *J* = 5.7, 9.4 Hz, 0.9H), 2.56–2.47 (m, 0.2H), 2.44–2.30 (m, 1.8H), 2.29–2.22 (m, 0.1H), 2.20–2.06 (m, 0.9H), 1.98–1.83 (m, 2H), 1.77–1.64 (m, 1H), 1.56–1.43 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: (219.1 *anti*) 218.5, 137.6 (137.3 *anti*), (128.9 *anti*) 128.8, 128.4, 127.9, (127.8 *anti*), 78.2 (77.1 *anti*), (51.4 *anti*) 50.4, 44.1 (43.9 *anti*), (39.2 *anti*) 38.6, 28.3 (26.9 *anti*), (20.5 *anti*) 20.2. Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 1 mL/min; λ = 220 nm, *R*t = 12.55 min (*syn major*) and 16.40 min (*syn minor*) and 19.41 min (*anti minor*) and 25.04 min (*anti major*).

General procedure for the Michael reaction of acetone with nitrostyrenes

A mixture of the catalyst **6** (0.01 mmol), acetic acid (0.02 mmol) in acetone (2 mmol) was stirred at room temperature for 5 min. To the resulting mixture was added nitroolefin (0.2 mmol) at room temperatiure. After the reaction was completed (monitored by TLC), the reaction mixture was purified by column chromatography on silica gel (100–200 mesh, hexane/ethyl acetate = 10:1–5:1) to afford desire product.

(*R*)-5-Nitro-4-phenylpentan-2-one (15a)[29-34]. White solid: yield 95%; 32% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.29 (m, 3H), 7.27–7.20 (m, 2H), 4.70 (dd, *J* = 6.8, 12.3 Hz, 1H), 4.60 (dd, *J* = 7.5, 12.3 Hz, 1H), 4.01 (t, *J* = 7.2 Hz, 1H), 2.92 (d, *J* = 7.0 Hz,

2H), 2.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.4, 138.8, 129.1, 127.3, 79.4, 46.1, 39.0, 30.4 ppm; Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 1 mL/min; λ = 210 nm, *R*t = 12.06 min (*minor*) and 13.12 min (*major*).

(*R*)-5-Nitro-4-(*p*-tolyl)pentan-2-one (15b)[33,34]. White solid: yield 89%; 18% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16–7.07 (m, 4H), 4.67 (dd, *J* = 7.5, 12.8 Hz, 1H), 4.57 (dd, *J* = 7.5, 12.8 Hz, 1H), 3.96 (t, *J* = 7.5 Hz, 1H), 2.89 (d, *J* = 6.8 Hz, 2H), 2.31 (s, 3H), 2.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.5, 137.5, 135.6, 129.7, 127.1, 79.5, 46.1, 38.6, 30.3, 21.0 ppm; Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 1 mL/min; λ = 210 nm, *R*t = 8.06 min (*minor*) and 8.92 min (*major*).

(*S*)-4-(Furan-2-yl)-5-nitropentan-2-one (15c)[32,34]. Light brown oil: yield 93%; 6% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.33 (m, 1H), 6.30–6.29 (m, 1H), 6.15–6.14 (m, 1H), 4.68 (dd, *J*=3.5, 6.3 Hz, 2H), 4.10 (t, *J* = 6.9 Hz, 1H), 2.98 (dd, *J* = 6.4, 18.0 Hz, 1H), 2.90 (dd, *J* = 7.5, 18.0 Hz, 1H), 2.18 (s, 3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.0, 151.6, 142.2, 110.4, 107.0, 77.0, 43.4, 32.8, 30.2 ppm; Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 1 mL/min; λ = 210 nm, *R*t = 12.44 min (*minor*) and 14.37 min (*major*).

(*R*)-4-(Naphthalen-1-yl)-5-nitropentan-2-one (15d)[32,33]. Light brown oil: yield 84%; 96% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.63–7.59 (m, 1H), 7.55–7.51 (m, 1H), 7.43 (t, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 7.0 Hz, 1H), 4.94 (t, *J* = 6.7 Hz, 1H), 4.79 (dd, *J* = 3.3, 7.5 Hz, 2H), 3.10 (dd, *J* = 7.5, 11.7 Hz, 2H), 2.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.5, 134.7, 134.1, 130.8, 129.2, 128.4, 126.9, 126.0, 125.2, 123.5, 122.2, 78.8, 45.9, 33.3, 30.2 ppm; Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 1 mL/min; λ = 220 nm, *R*t = 10.17 min (*major*) and 11.20 min (*minor*).

(*R*)-4-(4-Chlorophenyl)-5-nitropentan-2-one (15e)[32-34]. White solid: yield 92%; 28% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* =8 .5 Hz, 2H), 4.68 (dd, *J* = 6.6, 12.5 Hz, 1H), 4.57 (dd, *J* = 7.9, 12.5 Hz, 1H), 3.99 (t, *J* = 7.2 Hz, 1H), 2.90 (dd, *J* = 2.1, 7.0 Hz, 2H), 2.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.9, 137.3, 133.7, 129.2, 128.7, 79.1, 45.9, 38.3, 30.3 ppm; Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 1 mL/min; λ = 210 nm, *R*t = 10.52 min (*minor*) and 12.01 min (*major*).

(*R*)-4-(4-Methoxyphenyl)-5-nitropentan-2-one (15f)[32-34]. Light yellow solid: yield 93%; 22% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.66 (dd, *J* = 6.9, 12.2 Hz, 1H), 4.56 (dd, *J* = 7.8, 12.2 Hz, 1H), 3.95 (t, *J* = 7.3 Hz, 1H), 3.78 (s, 3H), 2.88 (d, *J* = 7.0 Hz, 2H), 2.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.5, 159.0, 130.6, 128.4, 114.4, 79.7, 55.1, 46.2, 38.3, 30.3 ppm; Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 1 mL/min; λ = 210 nm, *R*t = 11.93 min (*minor*) and 13.24 min (*major*).

(*R*)-5-Nitro-4-(4-(trifluoromethyl)phenyl)pentan-2-one (15g)[35]. Light brown solid: yield 90%; 26% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 4.73 (dd, *J* = 6.5, 12.6 Hz, 1H), 4.63 (dd, *J* = 8.1, 12.6 Hz, 1H), 4.09 (t, *J* = 7.2 Hz, 1H), 2.94 (dd, *J* = 2.6, 7.0 Hz, 2H), 2.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.7, 143.0, 127.9, 127.8, 126 (q, *J* = 3.6 Hz), 78.8, 45.8, 38.7, 30.9, 30.3 ppm; Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 1 mL/min; λ = 210 nm, *R*t = 13.62 min (*minor*) and 16.34 min (*major*).

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