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A new class of chiral pyrrolidine for asymmetric Michael addition reactions. New mechanism via simple 4+2 type attack of the enamine on the *trans*-nitrostyrene

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Abstract—A new chiral organocatalyst is described in this paper. A new mechanism for the overall Michael condensation of ketones with nitroolefins using our catalyst is suggested based on molecular modelling studies.
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1. Introduction

Numerous new methodologies in asymmetric synthesis have been developed by chemists over the last few years.[1] Recently, there has been enormous interest in the use of small organic molecules as catalysts instead of using asymmetric catalysts containing metals. Enantioselective organocatalysis using a chiral organic molecule is emerging as a powerful tool.[2] An enantioselective organocatalytic system that has been studied extensively[3] is based on proline, and has been found to accelerate a range of transformations such as aldol reactions,[4] Robinson annelations,[5] Mannich reactions,[6] conjugate additions,[7] α-aminations,[8] α-aminooxylations,[9] α-alkylations[10] and other reactions.[11] In order to improve the catalysts' profile many diamines and proline analogues have been designed as potential new catalysts for these types of reaction.[12] In the last few years there has been enormous interest in Michael addition using an organic catalyst.[13] Some molecules derived from proline, which have been used as catalysts to promote addition to nitrostyrenes, can be seen in Figure 1. Apart from proline, **1**, Ley's analogues **2**–**4**[14] have been used in the addition of cyclohexanone to *trans*-β-nitrostyrene; these replace the carboxylic acid of the proline by a tetrazole or an acyl sulfonamide. Similarly, some diamines have been found to work as catalysts, such as the one described by Barbas, **5**,[15] or that of Alexakis, **6**,[16] which have been used in the same reaction. Recently, Wang has used catalyst **7**,[17] not only in this reaction but also in other reactions such as α-sulfenylations,[18] α-selenylations[19] and other reactions.[20] Recently, catalysts **8** and **9**

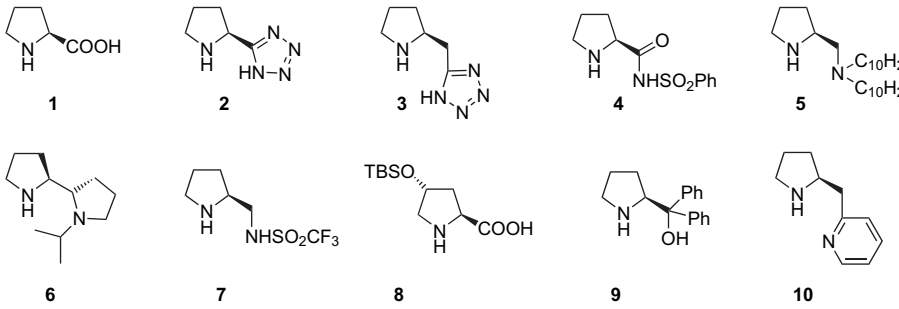

Figure 1. Organocatalysts used in the Michael addition of cyclohexanone to *trans*-β-nitrostyrene.

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have been used by Hayashi et al.[21] in the Michael addition of cyclohexanone to *trans*-β-nitrostyrene, and Kotsuki et al. have developed catalyst **10**.[22]

2. Results and discussion

These results prompted us to communicate our observations in this area. As can be seen, all the above catalysts are either monosubstituted in the pyrrolidine ring or disubstituted with a single protected hydroxyl group substituent. It is known that a subtle change in the functionalization of the core structure can improve the activity of the catalyst, so we decided to synthesize a catalyst with two hydroxyl groups at positions 3 and 4 of the pyrrolidine ring protected via a cyclic protecting group. The synthesis of catalyst **14** was achieved as shown in Scheme 1.

Epoxide **11** has been previously obtained by us in a simple way from easily available starting materials.[23] Our catalyst, **14**, was obtained in good yield using the reactions shown in Scheme 1.

The rationale behind our choice of the isopropylidene protected system was based on the observation that the catalysts shown in Figure 1 showed variability in the reaction of cyclohexanone with *trans*-β-nitrostyrene, low yields being obtained in many cases. Recently, the reaction of cyclohexanone and *trans*-β-nitrostyrene has been reported with Wang's catalyst in ^{i}PrOH.[24] Therefore, we decided to increase the solubility of the catalyst in nonpolar solvents by adding more functionality to the pyrrolidine ring, while maintaining the acidity of the sulfonamide and additionally rigidifying somewhat the core of the catalyst. In order to see what differences and possible advantages our catalyst **14** might have, we decided to do a comparative molecular modelling study with Wang's catalyst, **7**.

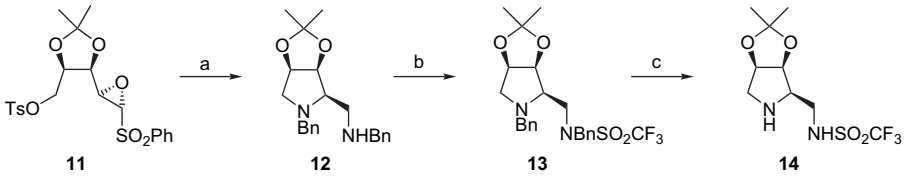
Two approaches were used. In the first, Wang's published transition states[24] for a ketone–enamine formed with **7** and pentan-3-one in the reaction with nitrostyrene from the *si* or *re* face, were imported into Sybyl v. 7.1 (Tripos, Inc., St. Louis, MO), modified to provide the equivalent complexes with our catalyst **14** as the cyclohexanone enamine derivatives, and subjected to constrained optimization using Jaguar v. 6.5 (Schrodinger LLC, New York, NY) (B3LYP/631G* DFT) with the distance between the atoms of the newly forming bond maintained constant. The resulting structures were then subjected to a standard transition-state optimization without constraints, and then Hessian matrix and vibrational modes were examined (only one negative vibrational frequency with absolute value $>20\ cm^{-1}$ corresponds to a stretch of the new bond) to confirm that a true transition state corresponding to the desired bond formation had been found. As in Wang's work, a water molecule was included in the calculation, though we were concerned that the presence of this water molecule would place a significant cost on the ternary transition state that was not fully taken into account in the relative energy calculations (particularly since the third molecule in the transition-state model was not the solvent). In the gas phase, the transition states showed that the B3LYP/6-31G* transition-state energies of the *si* and *re* attacks were as shown in Table 1.

While the energy difference is in the correct direction, favouring *re* attack, it is perhaps rather smaller than that might be desired.

The transition-state complexes were, therefore, subjected to transition-state geometry optimization calculations with vibrational frequency calculation using a Jaguar model for solvation (in chloroform, dielectric constant 4.806, density 1.489 g/mL) to test the hypothesis that the energy difference would be more marked in the presence of solvent. This method was unable to locate a true saddle point, even when input conformations were obtained by stepwise variation of the length of the newly forming bond from 1.95 to 2.25 Å (in 0.02 Å steps), and the energy maximum on that coordinate was used as the starting point for any one of the transition-state search algorithms available in Jaguar. Invariably, transition states for other processes were found. It may be that our catalyst prefers a mechanism different from that suggested by Wang for **7** that the nature of the substrate (cyclohexanone in our case, rather than an acyclic ketone as in Wang's work) affects the mechanistic preference, or it may be that the use of chloroform as solvent changes the preferred transition state, as such a nonpolar solvent would not favour the development of separation of charges required by simple Michael attack of the enamine on the nitroolefin. It is also possible that the differences in the Gaussian solvent model used by Wang and that used in Jaguar may account for the difference. In subsequent studies, we also compared 6-31G* with larger basis sets, but found no significant qualitative difference in our findings (only the results for the largest basis set tried are reported below).

Table 1. Computed energies of Wang-type transition-state complexes for the reaction of **14** with nitrostyrene and cyclohexanone

Stereochemistry of attack	*si*	*re*
SCF energy (hartrees)	−2284.00900	−2284.01296
Zero point energy (kcal/mol)	348.1	347.8
Gibbs free energy $Gtot_{298}$ (hartrees)	−2283.5224	−2283.5269
Free energy relative to minimum (kcal/mol)	2.8	0



11 12 13 14

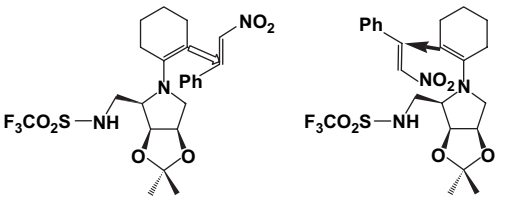
Scheme 1. Synthesis of catalyst **14**. Reagents and conditions: (a) (1) $BnNH_2$, MeOH, reflux; (2) $NaBH_4$, MeOH, 0 °C, 65%; (b) Tf_2O, Et_3N, CH_2Cl_2, 0 °C, 60%; (c) H_2, $Pd(OH)_2/C$, MeOH, rt, 90%.

Given the uncertainty in predictions that arose from the above models and our concern over the ternary transition state proposed by Wang, we sought to find other possible transition states that might obviate this requirement and give us results that were always consistent with the experimentally observed products.

We studied the process for the addition of the enamine derived from **14** and cyclohexanone to nitrostyrene, considering all eight possible approaches and generating initial geometries with force field methods to optimize all but the length of the newly forming bond, which was constrained to 2 Å (Fig. 2).

Thus, each putative global minimum energy conformation found was subjected to geometry optimization, using Jaguar (version 6.5) with B3LYP/6-31G** DFT, by scanning the bond length of the newly formed bond between 2.20 and 1.45 Å in 0.05 Å steps. By this means all but one of the possible approaches (the approach from the lower face—the face opposite the sulfonamide—giving rise to the *R*,*R* product) were found to show an apparent local maximum with the bond length of the newly formed bond around 2.00 Å, as expected. The bottom-face approach to give the *R*,*R* product showed just a monotonic increase in energy as the distance between the putative reacting centres was reduced.

Attempts were made to locate a transition state using the quadratic synchronous transit method available in Jaguar, using the same basis set as before and choosing the local energy maximum encountered in the earlier study as a model for the transition state and points on the bond-length scan either side of this maximum as models for the 'reactant' and 'product'. However, despite extensive attempts to find a good transition state with just one negative vibrational frequency, including the use of alternate transition-state search routines (the 'standard' method and the linear synchronous transit method implemented in Jaguar were both tried, and



Anti–enamine, lower face, phenyl-*endo* attack

Syn-enamine, upper face, phenyl-*exo* attack

Figure 2. Two representative approaches of the eight possibilities considered for the attack of nitrostyrene on the cyclohexanone-derived enamine (*syn* or *anti* enamine rotamer, upper or lower face attack, phenyl *endo* or *exo*).

where applicable searching was constrained to the lowest bond-stretch mode) and modelling the effect of solvent, greater accuracy in the SCF and/or using Hessian refinement on the first three low-frequency modes, no suitable transition states were identified. This is presumably why the water molecule was found to be necessary in the Wang transition-state models. However, geometry optimization starting from structures obtained from the above bond-length scanning study on the 'product' side of the local maximum gave rise directly, in most cases, to an unexpected intermediate, of the type shown in Figure 3.

It is known[25] that such cyclic intermediates can be isolated where the nitroolefin is α-substituted, but not otherwise, in which case the 'Michael adduct' is the main observed product. This could be either because the mechanism is indeed simple Michael addition (particularly in more polar media), or because the cycloadduct breaks down rapidly where there is no α substituent. Such intermediates have been proposed previously[26] in cases where there is a high level of stereocontrol in the addition of a nitroolefin to an enamine, and also in cases where they could not be isolated but were presumed to break down subsequently under the reaction conditions to give the observed products. In our case, these intermediates could be additionally stabilized by the presence of a possible hydrogen bond between the nitro group and the sulfonamide, and this would be expected if anything to increase the probability that they participate in the reaction process. We, therefore, felt that it would be valuable to demonstrate that, at least, the presence of this hypothetical intermediate at a critical point on the reaction path would be consistent with observations, even if we could not prove this to be the case unequivocally. Thus, we attempted to find similar structures derived from each possible approach of the reactants to see whether the experimental stereochemical outcome of the reaction was consistent with such transition-state-like intermediates.

Each starting structure was obtained by minimal adjustment in Maestro (v. 7.5.106; Schrodinger LLC, New York, NY) of the structures previously obtained by DFT minimization of the product-side bond scan study structures to the topology of the structures in Figure 3, followed by appropriate molecular mechanics conformational exploration and geometry pre-optimization. All the low-lying structures were then re-optimized with the B3LYP/6-31G** DFT using accurate SCF criteria and a solvent model for $CHCl_3$ (dielectric 4.806, density 1.489 g/mL). Further structures were generated in which alternate ring-flip conformations were studied, and, given the possible anomeric effect at the carbon bearing both nitrogen and oxygen substituents, both the axial-oxygen and axial-nitrogen ring-flips were tried.

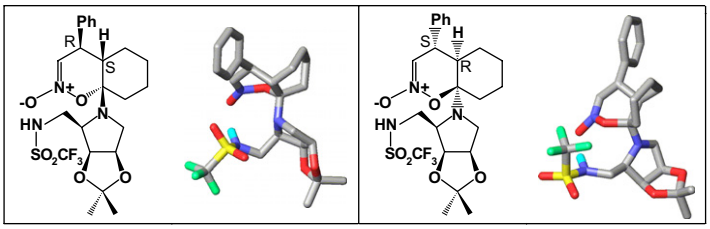


Figure 3. Left panel, *S*,*R* potential intermediate; right panel, *R*,*S* potential intermediate.

While in principle the Diels–Alder type process giving rise to this intermediate could (especially if not fully concerted[25] and partially reversible, as has been proposed previously[27]) give rise to any of the possible four diastereoisomeric products (ignoring the stereocentre at the hemiaminal centre, which would be lost, e.g., on in situ hydrolysis or on workup), the most likely transition-state-like intermediates based on accessible reactant conformations and the energies observed for the intermediates were those shown in Figure 3, giving rise to the *R*,*S* or *S*,*R* stereochemistry in the final product. These more promising candidates were subjected to a DFT geometry optimization study at the B3LYP/6-311G**+ level. The lower energy associated with the *S*,*R* intermediate (left panel, Fig. 3) is consistent with the observed preference for the *S*,*R* product (Tables 2 and 3). Neither putative intermediate showed any negative vibrational frequencies after optimization in either the gas phase or solvated model, confirming that these were intermediates and not transition-state structures.

If this intermediate is used to serve as a model for the transition state, the energy difference would be sufficient to account for the significant preference for the *S*,*R* product. It is also worth noting that the energetic favourability of the *S*,*R* intermediate was found consistently at every level of calculation tried, from molecular mechanics with MMFF94s to small basis set DFT, through the calculations described in detail here, with or without solvent model. The formation of a cyclic intermediate might also help to explain why the diastereoisomeric ratios were so good.

As can be seen, the axial-oxygen double-boat arrangements were those that have the lowest energy and were the most consistent with possible reaction mechanisms, arising via simple 4+2 type attack of the enamine on the *trans*-nitrostyrene in a concerted or near-concerted way, consistent with the nonpolar media that gave the best experimental results (see below). The boat has been identified as an important transition-state geometry of Diels–Alder reactions.[28]

We investigated experimentally, in some detail, the influence of the solvent in the 'Michael addition' of cyclohexanone to *trans*-β-nitrostyrene. As can be seen in Table 4, the reaction yields varied significantly in the solvents tested. It can be appreciated that chloroform is the solvent of choice,

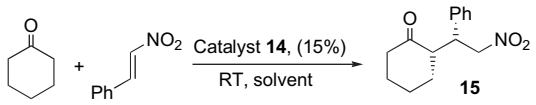
Table 2. Energies of the putative intermediates in gas phase

Stereochemistry	*S*,*R*	*R*,*S*
SCF energy (hartrees)	−2208.1574	−2208.1435
Zero point energy (kcal/mol)	331.8	331.2
Gibbs free energy $Gtot_{298}$	−2207.6927	−2207.6816
Free energy relative to minimum (kcal/mol)	0	7.0

Table 3. Energies of the putative intermediates with solvent model for $CHCl_3$

Stereochemistry	*S*,*R*	*R*,*S*
SCF energy (hartrees)	−2208.1774	−2208.1674
Zero point energy (kcal/mol)	350.1	350.3
Gibbs free energy $Gtot_{298}$	−2207.6839	−2207.6734
Free energy relative to minimum (kcal/mol)	0	6.7

Table 4. Solvent effect on the asymmetric Michael addition of cyclohexanone to *trans*-β-nitrostyrene



Entry[a]	Solvent	Yield (%)[b]	dr (%)[c]	ee (%)[d]
1	DMSO	41	>95	82
2	^{i}PrOH	24	>95	84
3	CH_2Cl_2	10	>95	80
4	$CHCl_3$	96	94	90
5	CH_3CN	5	>95	18
6	THF	5	>95	0

[a] For experimental conditions see Section 3.
[b] Yield of the isolated product.
[c] Determined by ^{1}H NMR spectroscopic analysis.
[d] Determined by chiral high-performance liquid chromatography (HPLC) analysis (Chiralpak OD-H).

a remarkable selectivity for this solvent being observed, while the yields in more polar solvents such as DMSO or ^{i}PrOH are moderate and in less polar solvents such as THF are very low. Chloroform is the solvent of choice as it gives the best yield with very good diastereo- and enantioselectivity (Table 4, entry 4); this contrasts sharply with Wang's catalyst where the yields and ees in ^{i}PrOH are superior to those in $CHCl_3$, and may support the idea of a change of mechanism.

With the optimal conditions in hand, we probed the scope of the reaction with a variety of nitroolefins and ketones in the presence of 15% of catalyst **14**, using chloroform as solvent at room temperature (20 °C) obtaining yields that vary from no reaction to high yields showing in all cases good diastereo- and enantioselectivity (Table 5).

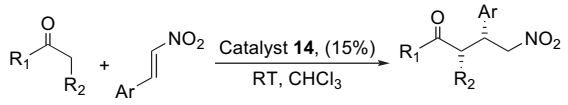
In conclusion, a new type of catalyst can be added to the variety of organocatalysts for asymmetric 'Michael addition' to nitroolefins, demonstrating a highly competitive profile in terms of convenience, stereoselectivity and yield. In this case the availability of extra functionality opens the way for further functionalization in order to increase the efficiency and selectivity in this kind of reaction. A detailed molecular modelling study, which led to the proposal of a new mechanism, via simple 4+2 type attack of the enamine on the *trans*-nitrostyrene, is included. Further studies, in order to extend the scope of this catalyst are in progress.

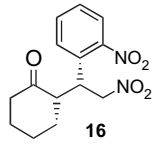
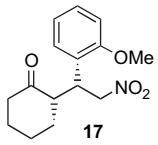
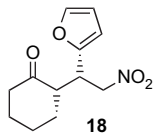
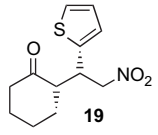
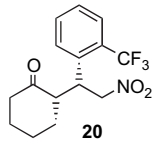
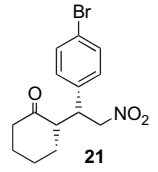
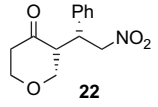
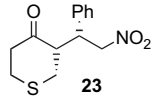
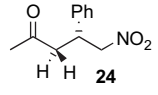
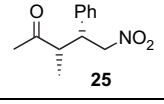
3. Experimental section

3.1. General

Unless otherwise stated, all chemicals were purchased, which have highest purity and commercially available, and were used without further purification. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200/400 and 50/75 MHz, respectively. The spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at 7.26 and 77.0 ppm, for ^{1}H and ^{13}C, respectively. Chemical shifts are reported in parts per million and coupling constants (*J*) are given in hertz. Diethyl ether, THF and benzene were distilled from sodium, and pyridine and dichloromethane were distilled under argon from CaH_2.

Table 5. Catalytic asymmetric Michael addition of ketones to different *trans*-β-nitrostyrenes catalyzed by **14**



Entry[a]		Yield (%)[b]	dr (%)[c]	ee (%)[d]
1	 **16**	46	>95	81
2	 **17**	62	>95	25
3	 **18**	60	>95	82
4	 **19**	45	>95	65
5	 **20**	42	>95	94
6	 **21**	70	>95	86
7	 **22**	65	>95	n.d.
8	 **23**	45	>95	94
9	 **24**	68	—	20
10	 **25**	65	>95	84

[a] For experimental conditions see Section 3.
[b] Yield of the isolated product.
[c] Determined by ^{1}H NMR spectroscopic analysis.
[d] Determined by chiral high-performance liquid chromatography (HPLC) analysis (Daicel Chiralpak AD).

3.2. (2*R*,3*S*,4*R*)-*N*-Benzyl-2-[(benzylamin(e)methyl]-3,4-isopropylidenedioxy-pyrrolidine (12)

To a solution of epoxysulfone **11** (700 mg, 1.49 mmol) in 15 mL of MeOH was added benzylamine (0.81 mL, 7.44 mmol). The mixture was heated under reflux for 12 h and then cooled to 0 °C and 56 mg (1.50 mmol) of $NaBH_4$ was added. The reaction mixture was stirred for 30 min at 0 °C. After that the mixture was diluted with 1 mL of water and extracted with EtOAc. The combined organic layers were washed with water and brine, and then dried over Na_2SO_4. The resulting residue was then purified by chromatography on silica gel (*n*-hexane/EtOAc, 1/1) to provide diamine **12** (341 mg, 65%). $[\alpha]_D^{20}$ −106.4 (*c* 1.10 in $CHCl_3$); IR (film) *ν*: 2934, 2793, 1495, 1454, 1379, 1208, 1153; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.34–7.25 (m, 10H, Ph), 4.66 (dd, ^3J(H,H)=5.2 Hz, ^4J(H,H)=6.6 Hz, 1H, CH), 4.56 (dd, ^4J(H,H)=4.4 Hz, ^3J(H,H)=6.6 Hz, 1H, CH), 3.97 (d, $^{1''}J$(H,H)=13.6 Hz, 1H, CH_2), 3.85 (s, 2H, CH_2), 3.20 (d, $^{1''}J$(H,H)=13.6 Hz, 1H, CH_2), 3.02 (d, $^{1'}J$(H,H)=11.4 Hz, 1H, CH_2), 2.97 (d, ^5J(H,H)=11.0 Hz, 1H, CH_2), 2.82 (dd, ^4J(H,H)=4.4 Hz, $^{1'}J$(H,H)=11.4 Hz, 1H, CH_2), 2.40 (m, 1H, CH), 2.03 (dd, ^4J(H,H)=4.4 Hz, ^5J(H,H)=11.0 Hz, 1H, CH_2), 1.50 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=140.6, 138.7, 128.8, 128.6, 128.4, 128.3, 127.1, 111.5, 81.1, 78.3, 67.5, 59.6, 57.5, 54.6, 47.8, 26.5, 25.8; EIMS *m*/*z* (%) 352 (M^++1, 100), 232 (80), 158 (15), 91 (100); HRMS (EI) *m*/*z* calculated for $C_{22}H_{28}N_2O_2$: 352.2151 (M^+); found: 352.2163.

3.3. (2*R*,3*S*,4*R*)-*N*-Benzyl-2-[(benzyl-trifluoromethanesulfonylamino)methyl]-3,4-isopropylidenedioxy-pyrrolidine (13)

To a solution of 341 mg (0.97 mmol) of diamine **12** and TEA (0.162 mL, 1.16 mmol) in 5 mL of CH_2Cl_2 at 0 °C was added dropwise (via syringe) trifluoromethanesulfonic anhydride (0.174 mL, 1.06 mmol). The resulting solution was stirred for 5 h at room temperature, then diluted with 20 mL of CH_2Cl_2 and washed with HCl (1 M) aqueous solution. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (*n*-hexane/EtOAc, 9/1) afforded a colourless oil, **13**, in 60% yield (281 mg). $[\alpha]_D^{20}$ −29.5 (*c* 0.90 in $CHCl_3$); IR (film) *ν*: 2950, 2654, 1450, 1389, 1310, 1100, 980; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.44–7.20 (m, 10H, Ph), 4.67 (d, ^4J(H,H)=10.6 Hz, 1H, CH), 4.58 (dd, ^3J(H,H)=10.6 Hz, ^4J(H,H)=4.6 Hz, 1H, CH), 4.42 (m, 2H, CH_2), 3.98 (d, $^{1''}J$(H,H)=13.8 Hz, 1H, CH_2), 3.69 (dd, $^{3'}J$(H,H)=14.9, 3.0 Hz, 1H, CH_2), 3.61 (d, $^{3'}J$(H,H)=14.9 Hz, 1H, CH_2), 3.12 (d, $^{1''}J$(H,H)=13.8 Hz, 1H, CH_2), 3.01 (d, ^5J(H,H)=11.4 Hz, 1H, CH_2), 2.54 (m, 1H, CH), 2.03 (dd, ^4J(H,H)=4.6 Hz, ^5J(H,H)=11.4 Hz, 1H, CH_2), 1.45 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=138.1, 135.1, 128.6, 128.2, 126.9, 111.4, 79.6, 78.0, 67.5, 59.4, 57.2, 53.4, 45.2, 26.2, 25.5; HRMS (EI) *m*/*z* calculated for $C_{23}H_{28}N_2O_4F_3S$: 485.1722 (M^++1); found: 485.1735.

3.4. (2*R*,3*S*,4*R*)-2-(Trifluoromethanesulfonylamino)-methyl-3,4-isopropylidenedioxy-pyrrolidine (14)

A solution of 281 mg (0.58 mmol) of triflate **13** in 6 mL of MeOH was hydrogenated in the presence of a catalytic

amount of 20% $Pd(OH)_2$/C with a H_2 balloon at room temperature for 16 h. The catalyst was filtered through a pad of Celite® and washed with MeOH. The product was purified by flash chromatography (*n*-hexane/EtOAc, 1/1) to give 156 mg (90%) of compound **14**. $[\alpha]_D^{20}$ −15.6 (*c* 0.80 in $CHCl_3$); IR (film) *ν*: 2964, 1627, 1453, 1375, 1189, 1068; ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.86 (br s, 1H, NH), 4.73 (dd, ^3J(H,H)=5.4 Hz, ^5J(H,H)=4.0 Hz, 1H, CH), 4.64 (dd, ^4J(H,H)=5.4 Hz, ^3J(H,H)=4.2 Hz, 1H, CH), 3.67 (dd, ^5J(H,H)=14.2 Hz, ^2J(H,H)=4.0 Hz, 1H, CH_2), 3.45 (dd, ^5J(H,H)=14.2, 8.0 Hz, 1H, CH_2), 3.18 (d, $^{1'}J$(H,H)= 13.6 Hz, 1H, CH_2), 3.04 (m, 1H, CH), 2.74 (dd, $^{1'}J$(H,H)= 13.6 Hz, ^2J(H,H)=4.0 Hz, 1H, CH_2), 1.47 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=111.7, 81.4, 81.1, 62.9, 52.3, 43.4, 25.8, 23.8; HRMS (EI) *m/z* calculated for $C_9H_{16}N_2O_4F_3S$: 305.0777 (M^++1); found: 305.0764.

3.5. Typical procedure for Michael addition reaction

To a suspension of catalyst **14** (10 mg, 15%) and 0.438 mL (4.40 mmol) of cyclohexanone in 3.5 mL of $CHCl_3$ was added 33 mg (0.22 mmol) of *trans*-β-nitrostyrene. The resulting mixture was allowed to stir at room temperature for 16 h, whereupon the reaction was quenched with saturated aqueous ammonium chloride (2 mL) and the aqueous layers were extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and evaporated in vacuo and the resulting residue was purified by flash column chromatography using ethyl acetate/hexane.

Compounds **15**,[29] **16**,[14a] **17**,[22] **18**,[14a] **19**,[22] **20**,[14a] **21**,[30] **22**,[14a] **23**,[7a] **24**[31] and **25**[32] are known.

3.5.1. (2*S*,1′*R*)-2-[1′-Phenyl-2′-nitro-ethyl]-cyclohexanone (15). Purified using flash column chromatography (*n*-hexane/EtOAc, 9/1) to give the title compound as a white solid (96%); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.34–7.16 (m, 5H, Ph), 4.93 (dd, $^{2'}J$(H,H)=12.5 Hz, $^{1'}J$(H,H)=4.5 Hz, 1H, CH_2), 4.60 (dd, $^{2'}J$(H,H)=12.5, 9.9 Hz, 1H, CH_2), 3.76 (m, 1H, CH), 2.69 (m, 1H, CH), 2.50–1.52 (m, 8H, $4CH_2$). HPLC: Daicel Chiralpak AD; hexane/^{i}PrOH: 0.45 mL min^{-1}; 230 nm: t_R (minor)=10.8 min; t_R (major)=13.1 min.

3.5.2. (2*S*,1′*R*)-2-[2′-Nitro-1′-(*o*-nitro-phenyl)-ethyl]-cyclohexanone (16). Purified using column chromatography (*n*-hexane/EtOAc, 7/3) to give the title compound as a yellow solid (46%); ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.12–7.50 (m, 4H, Ph), 4.99 (dd, $^{2'}J$(H,H)=13.1 Hz, $^{1'}J$(H,H)=4.4 Hz, 1H, CH_2), 4.71 (dd, $^{2'}J$(H,H)=13.1, 10.2 Hz, 1H, CH_2), 3.92 (m, 1H, CH), 2.74 (m, 1H, CH), 2.46–1.24 (m, 8H, $4CH_2O$). HPLC: Daicel Chiralpak AD; hexane/^{i}PrOH: 0.45 mL min^{-1}; 230 nm: t_R (major)=82.0 min; t_R (minor)=99.0 min.

3.5.3. (2*S*,1′*R*)-2-[1′-(*o*-Methoxyphenyl)-2′-nitroethyl]-cyclohexanone (17). Purified using flash column chromatography (*n*-hexane/EtOAc, 6/4) (62%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.25–6.84 (m, 4H, Ph), 4.83 (dd, $^{2'}J$(H,H)= 12.6 Hz, $^{1'}J$(H,H)=4.5 Hz, 1H, CH_2), 3.95 (m, 1H, CH_2), 3.84 (s, 3H, CH_3), 3.00 (m, 1H, CH), 2.44 (m, 1H, CH), 2.00–1.17 (m, 8H, $4CH_2$). HPLC: Daicel Chiralpak AD; hexane/^{i}PrOH: 0.45 mL min^{-1}; 230 nm: t_R (major)=21.8 min; t_R (minor)=24.1 min.

3.5.4. (2*S*,1′*R*)-2-[2′-Nitro-1′-(*o*-furanyl)-ethyl]-cyclohexanone (18). Purified using flash column chromatography (*n*-hexane/EtOAc, 9/1) to give the title compound as a white solid (60%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.29–6.17 (m, 3H, Ar), 4.70 (dd, $^{2'}J$(H,H)=12.5 Hz, $^{1'}J$(H,H)=9.3 Hz, 1H, CH_2), 4.65 (dd, $^{2'}J$(H,H)=12.5, 9.3 Hz, 1H, CH_2), 3.98 (m, 1H, CH), 2.67 (m, 1H, CH), 2.50–1.31 (m, 8H, $4CH_2$). HPLC: Daicel Chiralpak AD; hexane/^{i}PrOH: 0.45 mL min^{-1}; 230 nm: t_R (major)=10.3 min; t_R (minor)=12.3 min.

3.5.5. (2*S*,1′*R*)-2-[2′-Nitro-1′-(*o*-thiophenyl)-ethyl]-cyclohexanone (19). Purified using flash column chromatography (*n*-hexane/EtOAc, 8/2) to give the title compound as a white solid (45%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.21–6.87 (m, 3H, Ar), 4.89 (dd, $^{2'}J$(H,H)=12.6 Hz, $^{1'}J$(H,H)=4.8 Hz, 1H, CH_2), 4.67 (dd, $^{2'}J$(H,H)=12.6 Hz, $^{1'}J$(H,H)=9.3 Hz, 1H, CH_2), 4.15 (m, 1H, CH), 2.71 (m, 1H, CH), 2.58–1.35 (m, 8H, $4CH_2$). HPLC: Daicel Chiralpak AD; hexane/^{i}PrOH: 0.45 mL min^{-1}; 230 nm: t_R (major)=14.9 min; t_R (minor)= 13.1 min.

3.5.6. (2*S*,1′*R*)-2-[2′-Nitro-1′-(*o*-trifluoromethylphenyl)-ethyl]-cyclohexanone (20). Purified using flash column chromatography (*n*-hexane/EtOAc, 6/4) to give the title compound as a white solid (42%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.70–7.39 (m, 4H, Ph), 4.98 (dd, $^{2'}J$(H,H)=12.5 Hz, $^{1'}J$(H,H)=4.5 Hz, 1H, CH_2), 4.76 (dd, $^{2'}J$(H,H)=12.5, 9.9 Hz, 1H, CH_2), 4.03 (m, 1H, CH), 2.70 (m, 1H, CH), 2.50–1.26 (m, 8H, $4CH_2$). HPLC: Daicel Chiralpak AD; hexane/^{i}PrOH: 0.45 mL min^{-1}; 230 nm: t_R (minor)=6.8 min; t_R (major)=9.7 min.

3.5.7. (2*S*,1′*R*)-2-[2′-Nitro-1′-(*p*-bromophenyl)-2′-nitro-ethyl]-cyclohexanone (21). Purified using flash column chromatography (*n*-hexane/EtOAc, 7/3) to give the title compound as a yellow solid (70%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.62–7.03 (m, 4H, Ph), 4.95 (dd, $^{2'}J$(H,H)=4.6 Hz, $^{1'}J$(H,H)=12.4 Hz, 1H, CH_2), 4.58 (dd, $^{2'}J$(H,H)=10.0, 12.4 Hz, 1H, CH_2), 3.75 (m, 1H, CH), 2.44 (m, 1H, CH), 2.04–1.13 (m, 8H, $4CH_2$). HPLC: Daicel Chiralpak AD; hexane/^{i}PrOH: 0.45 mL min^{-1}; 230 nm: t_R (minor)=13.0 min; t_R (major)=20.1 min.

3.5.8. (2*S*,1′*R*)-2-[1′-Phenyl-2′-nitro-ethyl]-tetrahydropyran-4-one (22). Purified using flash column chromatography (*n*-hexane/EtOAc, 7/3) to give the title compound as a yellow solid (65%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.37–7.16 (m, 5H, Ph), 4.95 (dd, $^{1'}J$(H,H)=4.4 Hz, $^{2'}J$(H,H)=12.8 Hz, 1H, CH_2), 4.64 (dd, $^{2'}J$(H,H)=12.8, 9.8 Hz, 1H, CH_2), 4.20 (m, 1H, CH), 3.78–3.65 (m, 1H, CH), 3.26–2.4 (m, 6H, $3CH_2$). HPLC: Daicel Chiralpak AD; hexane/^{i}PrOH: 0.45 mL min^{-1}; 230 nm: t_R (minor)= not determined; t_R (major)=not determined.

3.5.9. (2*S*,1′*R*)-2-[1′-Phenyl-2′-nitro-ethyl]-tetrahydrothiopyran-4-one (23). Purified using flash column chromatography (*n*-hexane/EtOAc, 7/3) to give the title compound as a yellow solid (45%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.37–7.14 (m, 5H, Ph), 4.72 (dd, $^{2'}J$(H,H)=12.5 Hz, $^{1'}J$(H,H)=4.5 Hz, 1H, CH_2), 4.60 (dd, $^{2'}J$(H,H)=12.5, 10.0 Hz, 1H, CH_2), 3.99 (ddd, ^2J(H,H)=15.4 Hz, $^{2'}J$(H,H)= 10.6, 4.8 Hz, 1H, CH), 3.09–3.01 (m, 1H, CH), 3.0–2.9 (m, 2H, CH_2), 2.85–2.75 (m, 2H, CH_2), 2.55–2.40 (m, 2H,

CH_2). HPLC: Daicel Chiralpak AD; hexane/^{i}PrOH: 0.45 mL min^{-1}; 230 nm: t_R (major)=7.9 min; t_R (minor)=14.8 min.

3.5.10. (4*S*)-5-Nitro-4-phenyl-pentan-2-one (24). Purified using flash column chromatography (*n*-hexane/EtOAc, 7/3) to give the title compound as a yellow solid (68%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.34–7.23 (m, 5H, Ph), 4.65 (td, ^4J(H,H)=1.4, 7.0 Hz, 2H, CH_2), 4.00 (dd, ^5J(H,H)=1.4 Hz, ^3J(H,H)=7.8 Hz, 1H, CH), 2.92 (d, ^3J(H,H)=6.0 Hz, 2H, CH_2), 2.13 (s, 3H, CH_3). HPLC: Daicel Chiralpak AD; hexane/^{i}PrOH: 0.45 mL min^{-1}; 230 nm: t_R (major)=10.6 min; t_R (minor)=11.2 min.

3.5.11. (3*S*,4*R*)-3-Methyl-5-nitro-4-phenyl-pentan-2-one (25). Purified using flash column chromatography (*n*-hexane/EtOAc, 7/3) to give the title compound as a yellow solid (65%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.4–7.2 (m, 5H, Ph), 4.60 (dd, ^5J(H,H)=4.8, 1.8 Hz, 2H, CH_2), 3.72–3.60 (m, 1H, CH), 3.2–2.8 (m, 1H, CH), 2.2 (s, 3H, CH_3), 0.95 (d, $^{1'}J$(H,H)=7.3 Hz, 3H, CH_3). HPLC: Daicel Chiralpak AD; hexane/^{i}PrOH: 0.45 mL min^{-1}; 230 nm: t_R (major)=9.4 min; t_R (minor)=7.9 min.

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