

Enantio- and Diastereoselective Michael Addition Reactions of Unmodified Aldehydes and Ketones with Nitroolefins Catalyzed by a Pyrrolidine Sulfonamide

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Abstract: Chiral (*S*)-pyrrolidine trifluoromethanesulfonamide has been shown to serve as an effective catalyst for direct Michael addition reactions of aldehydes and ketones with nitroolefins. A wide range of aldehydes and ketones as Michael donors and nitroolefins as acceptors participate in the process, which proceeds with high levels of enantioselectivity (up to 99% *ee*) and diastereoselectivity (up to 50:1 d.r.). The methodology has been employed successfully in an efficient synthesis of the potent H₃ agonist Sch50917. In addition, a practical three-step procedure for the preparation of (*S*)-pyrrolidine trifluorometh-

anesulfonamide has been developed. The high levels of stereochemical control attending Michael addition reactions catalyzed by this pyrrolidine sulfonamide, have been investigated by using *ab initio* and density functional methods. Transition state structures for the rate-limiting C–C bond-forming step, corresponding to *re*- and *si*-face addition to the reactive conformation of the key enamine intermediates have

been calculated. Analysis of these structures indicates that hydrogen bonding plays an important role in catalysis and that the energy barrier for *si*-face attack in reactions of aldehydes to form 2*R*,3*S* products is lower than that for the *re*-face attack leading to 2*S*,3*R* products. In contrast, the energy barrier for *re*-face addition is lower than that for *si*-face addition in reactions of ketones. The computational results, which are in good agreement with the experimental observations, are discussed in the context of the stereochemical course of these Michael addition reactions.

Keywords: asymmetric catalysis • Michael addition • nitroolefin • organocatalysis • pyrrolidine sulfonamide

Introduction

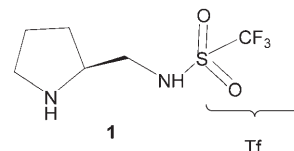
Herein, we describe the results of an investigation that proves the tenet that subtle changes in the structure of a cat-

alyst can sometimes significantly improve catalytic activity. As part of a recent, broad effort to search for novel organocatalysts, we have discovered that a L-proline surrogate, (*S*)-pyrrolidine trifluoromethanesulfonamide (**1**), promotes a variety of asymmetric organic transformations.^[1] Like L-pro-

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Supporting information for this article is available on the WWW under <http://www.chemeurj.org/> or from the author. It contains procedures for preparation of catalyst **1**, characterization of compounds **7a–7m** and **8a–8w** and computational results for stationary point geometries.



line, compound **1** exhibits high catalytic activity for Mannich^[1a] and α -aminoxylation^[1b] reactions that take place with high levels of enantioselectivity. In some cases, the catalytic activity of **1** is superior to that of L-proline. For example, much higher enantioselectivities are observed for asymmetric aldol reactions of α,α -dialkylaldehydes with aromatic aldehydes^[1c] and conjugate addition processes when **1** is used

as the catalyst.^[1d,e] Moreover, compound **1** serves as an effective catalyst for α -selenenylation^[1f] and α -sulfenylation^[1g] reactions, in which L-proline shows poor catalytic activity and in which more side products are generated. The enhanced catalytic activity, enantioselectivity, and/or diastereoselectivity associated with reactions promoted by **1** are a consequence of the acidic and sterically bulky properties of the NHTf group (Tf = trifluoromethanesulfonyl; respective pK_a in DMSO for NH_2Tf and CH_3CO_2H are 9.7 and 12.3).^[2] Furthermore, the lipophilic character and high stability of the NHTf group are responsible for the broad solvent compatibility of **1** and the need for only relatively low catalyst loadings.

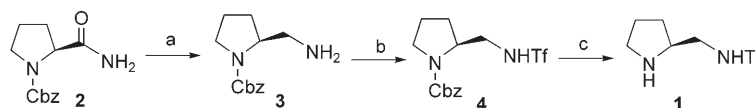
Michael addition reactions of nitroolefins with aldehydes and ketones are important methods for the synthesis of synthetically useful γ -nitrocarbonyl compounds, which serve as versatile building blocks for the preparation of complex organic targets.^[3,4] The nitro group in these substances can be readily converted into a variety of new functionalities including amines, nitrile oxides, ketones, and carboxylic acids.^[4b] In addition, the transformations of the aldehyde and ketone moieties into other useful functional groups are possible. Consequently, the development of catalytic, asymmetric versions of Michael addition reactions of nitroolefins with aldehydes and ketones is of great importance. Although several catalytic asymmetric processes have been reported, most require metal catalysts or restricted reaction conditions.^[5] Efforts aimed at achieving asymmetric versions of the process by using chiral organocatalysts have received great attention in recent years.^[6–14] Among them, processes promoted by L-proline and its derivatives have been extensively investigated.^[10–14] However, these works have led to mixed results in terms of enantio- and diastereoselectivities and substrate scope. Several pyrrolidine-based catalysts for asymmetric Michael reactions have been described, but moderate enantioselectivities are typically seen in these processes.^[10–14] In some cases, high enantio- and diastereoselectivities for the processes have been observed, but only for a narrow range of substrates. For example, Kotsuki and co-workers described a chiral pyrrolidine–pyridine catalyst that promotes highly enantio- and diastereoselective Michael addition reactions of ketones with nitrostyrenes.^[13] However, poor enantioselectivities (ca. 22% *ee*) were noted when an aldehyde was used as substrate. (*S*)-Diphenylprolinol silyl ether has been employed as a catalyst for this process and high levels of enantio- and diastereoselectivity are observed only when aldehydes are used as substrates.^[14]

In a recent preliminary publication,^[1e] we reported that pyrrolidine sulfonamide **1** serves as a catalyst for Michael addition reactions between aldehydes and β -nitrostyrenes; these reactions take place with high levels of enantioselectivity (89–99% *ee*) and diastereoselectivity ($\geq 20:1$ d.r.).

Herein, the results of studies aimed at exploring the full scope of this process are described. This effort has demonstrated that **1** catalyzes Michael additions of β -nitrostyrenes with both aldehydes and ketones, the process can be applied to an efficient synthesis of the biologically active potent H_3 agonist Sch50917, and ab initio and density functional theory calculations can be used to identify the source of the high levels of stereochemical control that attends these reactions.

Results and Discussion

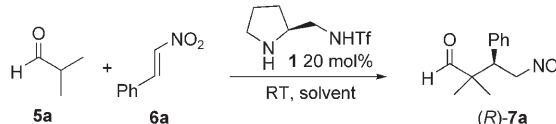
A three-step synthesis of (*S*)-pyrrolidine trifluoromethanesulfonamide (1**):** Organocatalyst **1** has been proven to be a valuable catalyst for a variety of organic reactions.^[1] Consequently, we have developed an efficient and practical method for its preparation. The key intermediate in the route is the *N*-Cbz-protected (Cbz = benzyloxycarbonyl) pyrrolidine primary amine **3** (Scheme 1). The only reported



Scheme 1. Three-step synthesis of (*S*)-pyrrolidine trifluoromethanesulfonamide (**1**). Reagents and conditions: a) BH_3 , THF, reflux, 7 h, 74%; b) Tf_2O , TEA, CH_2Cl_2 , 4.5 h, 76%; c) 10% Pd/C, H_2 , MeOH, 3 h, 93%.

method for the preparation of this substance is lengthy, inefficient, and time consuming, taking place in four steps with a low overall yield of 33% and requiring about one week of time.^[15] Also, it is important to point out that potentially explosive NaN_3 is used in the approach. We envisioned that a one-step synthesis of the amine **3** would be possible, starting with commercially available and cheap (*S*)-2-carbamoyl-1-*N*-Cbz-pyrrolidine (**2**)^[16] and relying on the direct amide-to-amine reduction reported by Brown and Curran (Scheme 1).^[17] In practice, treatment of **2** with BH_3 under the Brown–Curran conditions led to exclusive reduction of the amide group without affecting the Cbz protecting group in an optimized yield of 74%. Sulfonylation of the amine group in **3** with triflic acid anhydride (Tf_2O) in the presence of triethylamine (TEA) gave sulfonamide **4** (76%). It should be noted that slow addition of Tf_2O (over 1 h) at 0°C was needed to avoid formation of a bis-sulfonylation product. Finally the Cbz protecting group in **4** was removed by Pd-catalyzed hydrogenolysis (93%).

(*S*)-Pyrrolidine trifluoromethanesulfonamide (1**) catalyzed Michael addition reactions between aldehydes and nitroolefins:** The efficacy of (*S*)-pyrrolidine trifluoromethanesulfonamide (**1**) as an organocatalyst was initially evaluated using the reaction of isobutyraldehyde (**5a**) with *trans*- β -nitrostyrene (**6a**) at room temperature in *i*PrOH (Table 1, entry 1). This process occurred to smoothly form the Michael adduct **7a**, containing two simultaneously generated

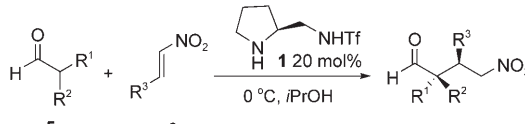
Table 1. Results of exploratory studies of **1**-promoted asymmetric Michael addition of isobutyraldehyde **5a** to *trans*- β -nitrostyrene **6a**.^[a]


Entry	Solvent	<i>t</i> [d]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	<i>i</i> PrOH	3	89	83
2	<i>i</i> PrOH ^[d]	4.5	85	90
3	DMSO	2	93	63
4	DMF	3	87	73
5	CH ₃ CN	3	64	73
6	CH ₃ NO ₂	3	37	71
7	THF	3	< 10	^[e]
8	1,4-dioxane	3	< 10	^[e]
9	CHCl ₃	3	43	79

[a] Reaction conditions: see Experimental Section. [b] Isolated yields. [c] Enantiomeric excess (*ee*) determined by chiral HPLC analysis (Chiralpak AS-H). [d] At 0 °C. [e] Not determined.

stereogenic and one quaternary carbon centers, in 89% yield and 83% *ee*.^[18] The absolute configuration of **7a** was determined to be *R*, by comparing the specific rotation of **7a** with that reported earlier for this substance.^[11a] An investigation of different reaction media revealed that solvent had a significant impact on the efficiency of this process. Reactions in polar solvents, such as *i*PrOH, DMSO, DMF, and CH₃CN (Table 1, entries 1–5), generally proceeded in higher yields, whereas those in less polar solvents (CH₃NO₂, THF, 1,4-dioxane and CHCl₃; entries 6–9) took place in low yields. Despite these differences, generally good to high enantioselectivities were associated with reactions conducted in all solvents, but those in protic (e.g., *i*PrOH) and acidic solvents (e.g., CHCl₃) gave highest enantioselectivities (entries 1 and 9). This is presumably due to participation of intermolecular hydrogen bonding between the solvent and oxygen of the CF₃SO₂ group, which stabilizes the favored transition state (see below). Lowering the reaction temperature to 0 °C led to further improvement in the enantioselectivity (up to 90%, entry 2) without significantly compromising the rate of the reaction. The results demonstrate that organocatalyst **1** displays a more broad solvent compatibility than proline as a result of the presence of the more lipophilic CF₃SO₂ group.

The scope and limitation of this catalytic process were explored next by using a wide range of aldehydes and nitroolefins. As summarized in Table 2, the reaction catalyzed by **1** has broad applicability with respect to aldehydes as Michael donors. Reactions of sterically demanding α,α -dialkyl aldehydes with *trans*- β -nitrostyrene (**6a**), although requiring longer reaction times, efficiently produced Michael adducts **7a–f** that contain quaternary carbon centers (Table 2, entries 1–6). Also, high enantioselectivities (89–93% *ee*) were observed for reactions with isobutyraldehyde and cyclopentanecarboxaldehyde (entries 1–4), and cyclohexanecarboxaldehyde afforded a product with moderate enantioselectivity (64%, entry 5). These observations suggest that substrate

Table 2. Enantioselective Michael reaction of aldehydes **5** with nitroolefins **6** in the presence of catalyst **1**.^[a]


Entry	Product 7	<i>t</i> [d]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]	d.r. (<i>syn/anti</i>) ^[d]
1	7a	4.5	85	90	–
2	7b	6	67	90	–
3	7c	6	75	89	–
4	7d	1.75	89	93	–
5	7e	4	42(79) ^[e]	64	–
6	7f	3	72	60(65) ^[f]	1.3:1
7	7g	1	77	97	12:1
8	7h	0.83	99	96	50:1
9	7i	1.16	63	94	22:1
10	7j	1	86	99	20:1
11	7k	1	94	99	30:1
12	7l	1.08	91	97	50:1
13	7m	1	76	22	50:1

[a] Reaction conditions: see Experimental Section. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H, or AD and Chiralcel OD-H). [d] Determined by ¹H NMR spectroscopy. [e] Based on recovered starting material. [f] Major diastereomer: 60% *ee*, minor isomer: 65% *ee*.

conformation plays an important role in governing the enantioselectivity of the process. The Michael addition reaction

of an unsymmetrically substituted α,α -dialkyl aldehyde also took place to give a Michael adduct (**7f**) in a good yield, but with relatively low *ee* and poor diastereoselectivity (entry 6). Studies with linear chain aldehydes revealed that these substrates reacted much more rapidly than the more hindered α,α -dialkyl aldehydes (entries 7–12). More significantly, reactions with β -nitrostyrenes, bearing both electron-withdrawing and electron-donating substituents, occurred with excellent levels of enantio- (94–99% *ee*) and diastereoselectivities ($\geq 20:1$ d.r., *syn* diastereomer major product). When the aliphatic *trans*-nitroolefin $\text{Ph}(\text{CH}_2)_2\text{CH}=\text{CHNO}_2$ was employed as substrate for the process, a high d.r. (50:1) but low *ee* (22%) was observed (Table 2, entry 13).

Direct (S)-pyrrolidine trifluoromethanesulfonamide (1**) catalyzed Michael addition reactions between ketones and nitroolefins:** As discussed above, previous studies of organocatalyzed Michael reactions with nitroolefins have shown that these processes take place with high levels of enantio- and diastereoselectivities, but they have a narrow substrate scope, working only for either aldehydes^[14] or ketones.^[13] An ideal catalytic system should be able to promote reactions of a broad spectrum of substrates. Accordingly, we tested the capacity of compound **1** to catalyze reaction of cyclohexanone with **6a** under the same reaction conditions (*i*PrOH, 0°C) found to be optimal for aldehydes. This process took place in a short time and almost quantitative yield, and with remarkably high enantio- (97% *ee*) and diastereoselectivity (50:1 d.r.) (Table 3, entry 1).

The generality of Michael addition reactions between ketones and nitroolefins promoted by **1** was explored. As the data in Table 3 show, the ring size of cyclic ketones strongly affects the reaction rate (entries 1–3). Excellent levels of enantio- (97% *ee*) and diastereoselectivity (50:1 d.r.) accompanied reactions of cyclohexanone, but, in contrast, almost no reaction occurred for five- and seven-membered ring cyclic ketones, presumably due to the difficulty of formation of enamines. A wide range of cyclohexanone derivatives efficiently reacted with *trans*- β -nitrostyrenes to give the Michael adducts with high levels of stereochemical control (86–99% *ee* and $\geq 30:1$ d.r. favoring *syn* diastereomers) (Table 3, entries 4–14). More significantly, β -nitrostyrenes possessing either electron-donating or electron-withdrawing groups on their aromatic ring underwent this process (entries 4–9). The electronic nature of substituents on the nitroolefins has no effect on stereoselectivity (entries 4–6); excellent levels of enantio- (96–99% *ee*) and diastereoselectivities (50:1 d.r.) are observed. The substitution pattern of β -nitrostyrenes influences enantioselectivities, but not diastereoselectivities. For example, when a CF_3 group is present at the *ortho*-position of β -nitrostyrene, a high d.r. (50:1), but a relatively low *ee* (88%) is observed (entry 7). Finally, the absolute configuration of **8a** was determined to be *2S,3R* by comparing its optical rotation, which is opposite to that of the known *2R,3S* aldehyde.^[13] Furthermore, the *syn* configuration of **8i** was determined by X-ray crystallographic analysis (Figure 1).^[19]

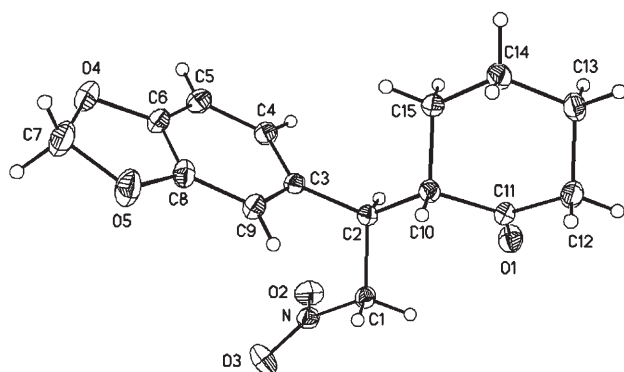
Table 3. Results of organocatalyst **1** promoted Michael addition of cyclic ketones to *trans*- β -nitrostyrenes.

Entry	Product 8	<i>t</i> [h]	Yield [%] ^[a]	<i>ee</i> [%] ^[b]	d.r. (<i>syn/anti</i>) ^[c]
1		10	96	97	50:1
2		72	11	n.d. ^[d]	n.d. ^[d]
3		168	7	n.d. ^[d]	n.d. ^[d]
4		24	84	96	50:1
5		16	92	98	50:1
6		24	83	99	50:1
7		34	70	88	50:1
8		36	79	86	30:1
9		48	91	98	50:1
10		24	87	98	50:1
11		12	95	97	30:1

Table 3. (Continued)

Entry	Product 8	<i>t</i> [h]	Yield [%] ^[a]	<i>ee</i> [%] ^[b]	d.r. (<i>syn/anti</i>) ^[c]
12		24	83	96	50:1
13		18	81	95	50:1
14 ^[e]		48	93	99	50:1
15		96	< 5	n.d. ^[d]	n.d. ^[d]
16		168	< 5	n.d. ^[d]	n.d. ^[d]
17		168	< 5	n.d. ^[d]	n.d. ^[d]

[a] Isolated yields. [b] Determined by chiral HPLC analysis (Chiralpak AS-H, or AD and Chiralcel OD-H). [c] Determined by ¹H NMR spectroscopy. [d] Not determined. [e] Mixture of DMF/*i*PrOH (1/1, v/v) used.

Figure 1. X-ray crystal structure of **8i**.

In addition, a wide range of cyclohexanone substrates, bearing various functionalities (entries 10–14) participate in **1**-catalyzed Michael addition reactions with nitrostyrenes and excellent levels of enantio- and diastereoselectivity (95–99% *ee* and $\geq 30:1$ d.r.) are observed. Moreover, the mild reaction conditions needed for this process are compatible with substrates bearing acid sensitive groups (e.g., ketals) and highly functionalized γ -nitro ketones bearing two stereogenic centers can be produced in a completely stereo-

controlled manner (entries 13–14). Unfortunately, α,α -dimethylcyclohexanone, 1-indanone, and α -tetralone failed to undergo reaction under these conditions (entries 15–17).

In this investigation, we also probed reactions of acyclic ketones with β -nitrostyrenes promoted by organocatalyst **1**. Under the reaction conditions described above, reaction of acetone with *trans*- β -nitrostyrene proceeded remarkably fast (8 h) to afford adduct **8r** in 96% yield and with a moderate enantioselectivity (55% *ee*; Table 4, entry 1). This is the

Table 4. Results of organocatalyst **1** promoted Michael addition of acyclic ketones to *trans*- β -nitrostyrenes.

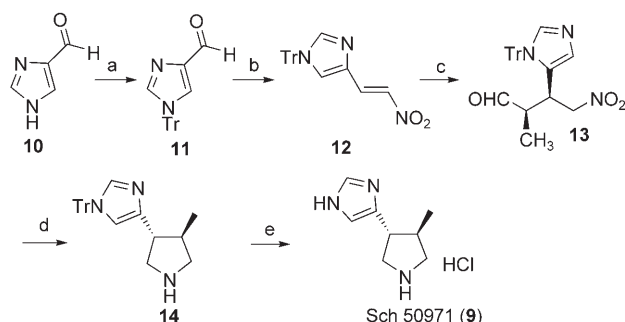
Entry	Product 8	<i>t</i> [h]	Yield [%] ^[a]	<i>ee</i> [%] ^[b]	d.r. (<i>syn/anti</i>) ^[c]
1		8	96	55	–
2		36	85	93	50:1
3		72	47	53	1.1:1
4		48	72	77	50:1
5		48	46	46	3:1
6		18	89	86	14:1

[a] Isolated yields. [b] Enantiomeric excess (*ee*) determined by chiral HPLC analysis (Chiralpak AS-H). [c] Determined by ¹H NMR spectroscopy.

highest % *ee* achieved for organocatalyzed reaction of acetone thus far.^[20] 3-Pentanone reacted with *trans*- β -nitrostyrene with excellent enantio- (93% *ee*) and diastereoselectivity (50:1; Table 4, entry 2). Reactions of unsymmetric ketones took place at the more substituted sites, presumably because the intermediate enamines were produced under thermodynamic control (entries 3–6). 2-Butanone gave product **8t** in 53% *ee* and poor diastereoselectivity (1.1:1 d.r., entry 3). By increasing the size of the ketone side chain, both the enantio- and diastereoselectivity of the Michael addition process were significantly improved (Table 4, entry 4). The same trend is also observed for α -hydroxyl ketone and its more bulky, protected silyl ether (entries 5 and 6). For example, 86% *ee* and 14:1 d.r. was achieved for reaction of TBDMS protected α -hydroxyl acetone (entry 6). To our knowledge the organocatalyzed processes described

above represent the first examples of efficient asymmetric Michel addition reactions of acyclic ketones to β -nitrostyrenes.^[10–14]

Synthesis of Sch 50971: Sch 50971 (**9**) is a potent H_3 agonist with potential use for the treatment of a variety of diseases including obesity, Alzheimer's disease, and attention deficiency/hyperactivity (Scheme 2).^[21,22] This substance was



Scheme 2. Total synthesis of Sch 50971 (**9**). Conditions: a) TrCl, TEA, CH_2Cl_2 , RT, 14 h, 95%; b) CH_3NO_2 , piperidine, AcOH, RT, 8 h, 79%; c) propionaldehyde, $iPrOH/CH_2Cl_2$ (v/v 1:1) 20 mol % **1**, 0°C, 24 h, 99% ee, 20:1 d.r., 78%; d) 20% Pd(OH)₂, MeOH, 45 psi, RT, 96 h, 65%; e) 95% TFA, 3 h, 91%.

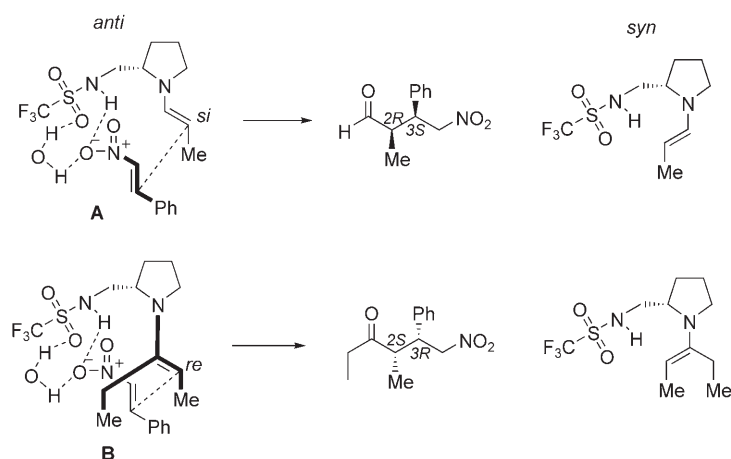
prepared earlier by applying an Evan's auxiliary controlled Michael addition reaction as a key step.^[21] However, only a 88% d.r. was achieved in this process and, as a result, an additional crystallization was needed in order to obtain enantiomerically pure material. We have designed a route to this target that relies on asymmetric Michael addition reaction of nitroolefin **12** to propionaldehyde catalyzed by **1** as a key step.

A synthetic route for preparation of Sch 50971, starting from commercially available 1H-imidazole-4-carboxaldehyde (**10**), is shown in Scheme 2. N-Protection of imidazole of **10** was achieved by reaction with TrCl (Tr=trityl) in the presence of TEA (95%). Condensation of aldehyde **11** with nitromethane in the presence of piperidine and acetic acid provided the desired *trans*-nitroolefin **12** in 79% yield. Michael addition of **12** to propionaldehyde, in the presence of 20 mol % **1** at 0°C afforded adduct **13** in 78% yield. In this reaction, a mixture of $iPrOH/CH_2Cl_2$ instead of $iPrOH$ was used as solvent, owing to the poor solubility of **12** in $iPrOH$. Essentially one enantiomer of **13** (99% ee) was obtained, but with relatively low d.r. (12:1). After silica gel column purification, the d.r. of the major, desired diastereomer **13** was increased to 20:1. One-pot transformation (65%) of γ -nitro aldehyde **13** into pyrrolidine **14** was promoted by Pd-catalyzed hydrogenation. Finally, the Tr group was removed by treatment with trifluoroacetic acid (TFA) as its HCl salt (91%). Comparing the optical rotation of synthetic Sch 50971 with that reported ($[\alpha]_D^{25} = +36.1$ ($c = 0.6$ in MeOH), literature value^[21] $[\alpha]_D^{25} = +43.5$ ($c = 0.34$ in MeOH)) indicates that

synthesized Sch 50971 has the correct absolute configuration. The lower optical rotation of the synthesized Sch 50971 is due to the presence of its minor diastereomer, resulting from the Michael addition reaction step.

Mechanistic study: The mechanism of (*S*)-pyrrolidine trifluoromethanesulfonamide **1** catalyzed Michael addition reactions of ketones and aldehydes with β -nitrostyrene should be similar to that for direct aldol reactions catalyzed by L-proline, which has been studied earlier by using theoretical methods.^[23] In the first step, the catalyst and the aldehyde or ketone substrates react to form enamine intermediates.^[1f,24] Stereochemistry of the overall process is believed to be determined by the addition of *trans*- β -nitrostyrene to these enamine intermediates.^[1e,f] The bulky sulfonamide group and the hydrogen bonding between the NH group of pyrrolidine sulfonamide and the nitro group of β -nitrostyrene are considered to be important to the high catalytic activity and enantio- and diastereo-selectivity of the catalyzed reactions.^[1e]

Representative transition state models **A** and **B** (Scheme 3) for reactions of energetically favored *anti*-enamines, formed from **1** and aldehydes (e.g., propanal) and ke-



Scheme 3. Proposed transition state models **A** and **B**.

tones (e.g., pentanone), are proposed to account for the high enantio- and diastereoselectivity of these Michael addition reactions. In both, the nitro group of *trans*- β -nitrostyrene is directed toward the CF_3SO_2NH group by two hydrogen bonds, an intramolecular $CF_3SO_2N-H\cdots O-N=O$ and an intermolecular $O=S=O\cdots H-O-H\cdots O-N=O$ involving solvent participation. As observed, *2R,3S* configurations are generated in reactions of aldehydes, while *2S,3R* products derive from ketones. We speculate that the *2R,3S* configuration results from a *si*-face attack, whereas the *2S,3R* stereochemical outcome comes from a preferred *re*-face addition to the ketone-derived enamine. This difference is presumably due to the steric hindrance induced by the ketone side chain (e.g., Et group), which leads to less hindered *re* face

approach. It is noted that there is a certain amount of controversy in proposing transition-state models to explain the stereochemistry observed in the Michael addition reactions of aldehydes and ketones with olefines. Enders proposed an *anti*-enamine, resulting from ketone for *re* face addition to nitroolefin.^[10b] However, Barbas III,^[11d] Alexakis et al.,^[11f] and Kotsuki,^[13] developed a *syn*-enamine for the ketone for *re*-face-attacking nitroolefin. In addition, a *si*-face addition of *anti*-enamine for aldehyde to nitroolefin was postulated by Barbas III^[11d] and Alexakis et al.^[11f]

To gain a more detailed understanding of the origin(s) of the high enantio- and diastereoselectivity of the processes catalyzed by **1** and the opposite stereochemistry associated with aldehydes and ketones, computational studies were first carried out by employing *ab initio* methods and density functional theory (DFT). For these treatments, we assume that the enamine formation is a fast process and thus has no bearing on the rate and stereoselectivity of the overall reaction.^[25] The subsequent hydrolysis step to recover the catalyst is also considered to involve a low-energy barrier.^[1f] As a result, the rate-limiting C–C bond-forming step involves formation of the activated reaction complex composed of the enamine intermediate and β -nitrostyrene. To simplify the calculations, we have used propanal and 3-pentanone to represent the aldehyde and ketone substrates, respectively. In addition, a water molecule instead of *i*PrOH is included in our transition-state models to provide hydrogen-bond interactions between the sulfonamide group in the catalyst and the nitro group in β -nitrostyrene. This is justified by the fact that water is produced in the formation of enamine intermediate.

To gain insight into the factors that can affect catalysis and stereochemistry, we have determined the energies and structures of reactant complexes and transition states using both *ab initio* and DFT methods. The geometric and energetic parameters are listed in Table 5 and structures are displayed in Figures 2 and 3.

The enamine intermediates can adopt *anti* and *syn* conformations as shown in Scheme 3. Similar to the results of studies on proline-catalyzed aldol reactions,^[23b,d,e] we found that the rate-limiting reaction barriers

for *syn*- enamines are much higher in energy than those for *anti*- enamines. Therefore, only the results for calculations on pathways arising from the *anti*-conformation are presented here. Two possibilities exist for the approach of β -nitrostyrene to the *anti*-enamine, one from the *si* face of the enamine and the other from the *re* face (Figures 2 and 3). These two approaches result in formation of the *2R,3S* and *2S,3R* products, respectively.

As shown in Table 5, the *re*-face arrangement of the reactant complex has a lower energy than its *si* counterpart no matter what type of substrate is involved. For example, the *si* complex for 3-pentanone-enamine and β -nitrostyrene is approximately 4 kcal mol^{−1} higher in energy.

The HF energy barriers for rate-limiting addition to the propanal enamine intermediate are 33.45 kcal mol^{−1} for the *si*-face attack and 34.92 kcal mol^{−1} for the *re*-face attack. Thus, there is a significant preference for formation of the *2R,3S* product, in accord with the experimental observation.^[1e] This preference is also observed in the B3LYP results, in which the respective *si*- and *re*-face addition barrier heights are 13.99 and 16.51 kcal mol^{−1}, respectively. The

Table 5. Hartree-Fock and DFT results for the rate-limiting C–C bond formation step of the Michael addition reaction of propanal and 3-pentanone to *trans*- β -nitrostyrene catalyzed by (*S*)-pyrrolidine sulfonamide **1**.

	<i>si</i> face (<i>2R, 3S</i>)		<i>re</i> face (<i>2S, 3R</i>)	
	reactant complex	transition state	reactant complex	transition state
propanal				
energy [kcal mol ^{−1}] (barrier height given in parentheses)				
HF/6-31G* opt + ZPE	0.44	33.89 (33.45)	0	34.92
B3LYP/6-31G*opt + ZPE	1.73	15.72 (13.99)	0	16.51
B3LYP/6-31G* + PCM	0.72	8.26 (7.54)	0	9.38
distances [Å] (HF results given in parentheses)				
N2–H...O1	1.87 (2.00)	1.80 (1.95)	1.85 (2.01)	1.74 (1.86)
O1...H–O–H	4.03 (4.00)	1.93 (2.08)	3.03 (3.87)	1.96 (2.07)
S=O...H–O–H	1.99 (2.13)	2.07 (2.23)	2.09 (2.09)	2.31 (2.55)
C2...C3	5.42	2.04	5.48	2.07
N1...N3	4.61	2.94	4.05	3.18
charges [e]				
N1/N3	−0.429/+0.441	−0.380/+0.394	−0.421/+0.450	−0.382/+0.412
O1/O2	−0.430/−0.395	−0.539/−0.481	−0.441/−0.393	−0.540/−0.483
3-pentanone				
energy [kcal mol ^{−1}] (barrier height given in parentheses)				
HF/6-31G* opt + ZPE	4.86	42.37 (37.51)	0	34.39
B3LYP/6-31G*opt + ZPE	3.83	22.26 (18.43)	0	16.24
B3LYP/6-31G* + PCM	4.43	15.47 (11.04)	0	8.94
distances [Å] (HF results given in parentheses)				
N2–H...O1	1.89 (1.99)	1.77 (1.89)	1.91 (2.65)	1.79 (1.94)
O1...H–O–H	2.89 (3.21)	1.92 (2.06)	2.56 (3.83)	2.02 (2.08)
S=O...H–O–H	1.99 (2.12)	2.38 (2.48)	2.05 (2.26)	2.20 (2.49)
C2...C3	4.91	2.08	5.88	2.11
N1...N3	5.02	3.00	4.57	3.22
C5...C β	3.81	3.12	3.86	3.68
C5...N2	3.63	3.33	3.52	3.24
C5...SO ₂	4.11	3.80	4.62	4.44
C5–H...H ₂ C β	2.88/4.36	2.09/3.42	3.88/4.20	3.65/3.78
charges [e]				
N1/N3	−0.473/+0.439	−0.455/+0.392	−0.472/+0.440	−0.455/+0.409
O1/O2	−0.442/−0.392	−0.536/−0.474	−0.441/−0.390	−0.535/−0.475
dihedral angle [°]				
C5–C1–C α –C β	43.6	−1.6	−102.9	−80.1

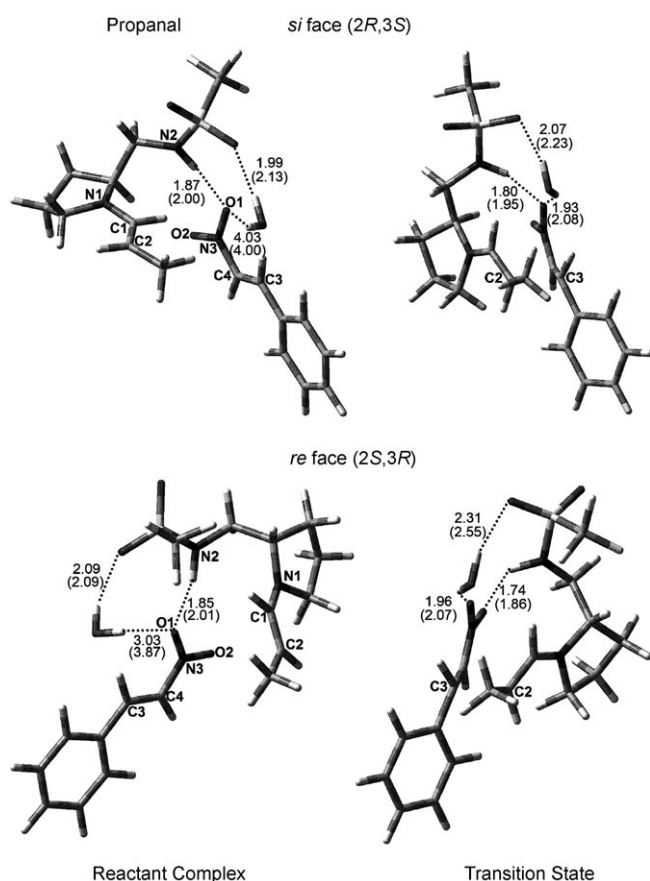


Figure 2. Geometries of stationary points in the rate-determining C–C bond-formation step of the catalyzed Michael addition reaction of propenal with *trans*- β -nitrostyrene obtained at the B3LYP/6–31G* level of theory (hydrogen bonds are represented by thin dashed lines).

lower barrier heights in the DFT results can be attributed to partial inclusion of the electron correlation effects. The normal mode associated with the sole imaginary frequency mainly involves the motion of C2 and C3, corresponding to the formation of a C–C bond between the enamine and β -nitrostyrene. The addition of solvent further decreases the barriers to 7.54 and 9.38 kcal mol^{–1}, due apparently to the stabilization of the polar transition states. The lowering of the reaction barrier in solution is consistent with the experimental observation that the reaction is accelerated in polar solvents. All the results indicate that the reactive path associated with the *si*-face attack by β -nitrostyrene to the propenal-enamine is more favorable than that associated with the *re*-face attack.

On the other hand, the energy barrier for the 3-pentanone-enamine reaction with β -nitrostyrene follows an opposite trend. The HF barriers for the *si* and *re* approaches are 37.51 and 34.39 kcal mol^{–1}, respectively, and the corresponding values obtained from the DFT calculations are 18.43 and 16.24 kcal mol^{–1}, respectively. Like in the aldehyde case, the reaction coordinate at the transition state involves primarily the formation of the C2–C3 bond. The preference of the 2*S*,3*R* product is also consistent with experimental observa-

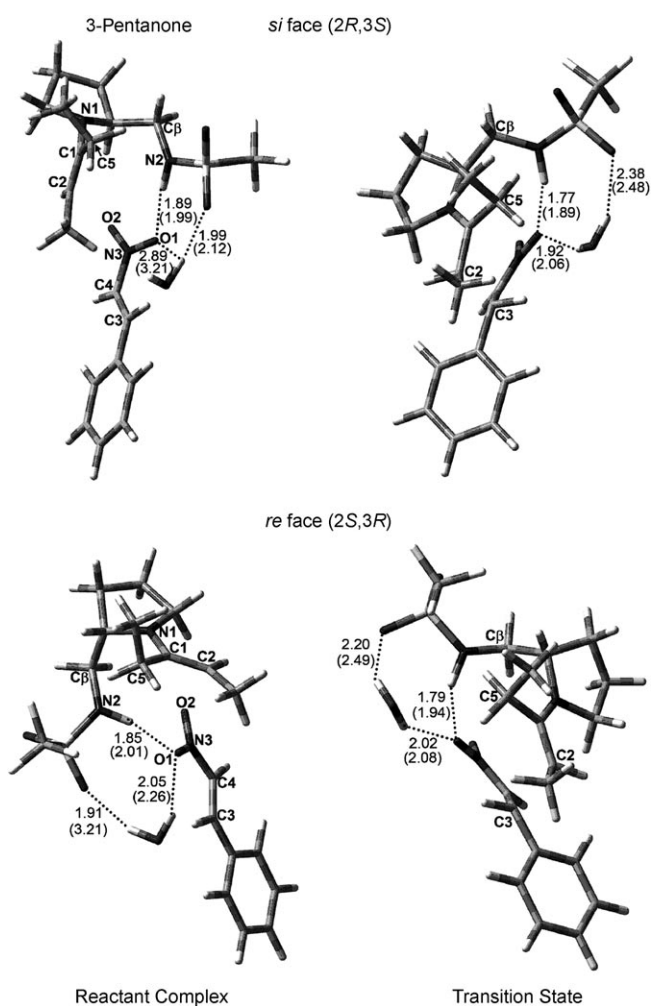


Figure 3. Geometries of stationary points in the rate-determining C–C bond-formation step of the catalyzed Michael addition reaction of 3-pentanone with *trans*- β -nitrostyrene obtained at the B3LYP/6–31G* level of theory (hydrogen bonds are represented by thin dashed lines).

tions discussed above. This picture is not changed when solvent effects are considered, resulting in barrier heights of 11.04 and 8.94 kcal mol^{–1}.

From the structure of the reactant complexes and transition states, it is clear that hydrogen-bonding interactions play a key role in the catalysis. As shown in Figures 2 and 3, the N2–H group of the sulfonamide forms a strong hydrogen bond with the O1 atom in the nitro group of β -nitrostyrene, whereas a water (solvent) molecule is hydrogen bonded with an oxygen atom in the sulfonamide group. For propenal-enamine complexes, the N2–H...O1 hydrogen bond length is 1.87 and 1.85 Å in the *si* and *re* arrangements, respectively, and the corresponding values for the hydrogen bond between water and sulfonamide are 1.99 and 2.09 Å, respectively. Apparently, the former interaction is stronger, presumably due to the acidity of the NH proton and the negative charges carried by the NO₂ oxygen. Similar hydrogen-bonding patterns are seen for the 3-pentanone-enamine complexes, in which the N2–H...O1 hydrogen bond length is

1.89 and 1.91 Å in the *si* face and *re* conformations, respectively, and the water–sulfonamide values are 1.99 and 2.05 Å, respectively.

At transition states, hydrogen bonds are generally strengthened, due apparently to increased oxygen charges in the nitro group of β -nitrostyrene as the two C=C bonds are broken. For propanal, the charge on the oxygen atom changes from -0.430 (-0.441) in the reactant complex to -0.539 (-0.540) in the *si* transition state. As a result, the N2–H $\cdots$ O1 hydrogen bond length is shortened to 1.80 and 1.74 Å in the *si* and *re* approaches, respectively. Similarly, the corresponding hydrogen bond length is reduced to 1.77 and 1.79 Å, respectively, for 3-pentanone, resulting from the negative charge buildup ($q = -0.094$ for both *si* and *re* reactions) at the nitro oxygen atoms. The role played by intramolecular hydrogen bonds in organocatalysis has long been recognized.^[1f,23a,d,e]

More interestingly, the water molecule develops a strong hydrogen-bond interaction with O1 of the NO₂ group, while maintaining hydrogen bonding with the sulfonamide group. As shown in Figures 2 and 3, the HO–H $\cdots$ O1 hydrogen bond length is 1.93 and 1.96 Å at the *si* and *re* transition states, respectively, for the propanal reaction and 1.92 and 2.02 Å, respectively, for the 3-pentanone reaction. The participation of water-assisted, intermolecular hydrogen bonds observed here underscores the importance of the sulfonamide group in the catalysis, which not only provides an electron-withdrawing force to the neighboring NH group, but also electrostatic interaction with the nitro group of β -nitrostyrene through a water molecule. Such a cooperative hydrogen-bond network resembles the “oxyanion hole” commonly found in enzymes for stabilizing the transition state.^[26]

It is much more difficult to unequivocally identify the source of the stereoselectivity in these catalyzed reactions. Hence, we only offer here some tantalizing evidence based on the structure of the transition states, which might suggest possible explanations. It appears that the origin of the stereoselectivity is quite different for the aldehyde and ketone substrates. In the former case, it appears that the energy difference in the transition state correlates with the distance between the negatively charged nitrogen atom (N1) in the pyrrolidine ring and the positively charged nitrogen atom (N3) in the nitro group of β -nitrostyrene. The N1–N3 distance at the *re* transition state (3.18 Å) is much larger than that at the *si* transition state (2.94 Å), rendering a stronger electrostatic interaction in the latter case. The larger N1–N3 distance at the *re* transition state is apparently due to the chirality at the C α position of the catalyst, which pointing the bulkier sulfonamide group towards the approach β -nitrostyrene. In the *si* approach, however, such stereo-hindrance is absent.

The opposite stereoselectivity for the Michael addition of ketones is most likely due to the bulky alkyl group that replaces the hydrogen in aldehydes, which might cause strong stereo hindrance at the transition state. Indeed, such hindrance can be readily found in the transition state structures

displayed in Figure 3, in which an ethyl group is much closer to the sulfonamide group in the *si* transition state than in the *re* counterpart. This is evidenced by the corresponding C5–C β distances of 3.12 and 3.68 Å and by other distances between various atoms belonging to the two groups as listed in Table 5. The stereo hindrance is further illustrated by the C5–C1–C α –C β dihedral angle, which shows that the *re* transition state is much closer to *gauche* (-80.1°) than the *si* transition state (-1.6°).

Conclusion

In conclusion, we have shown that (*S*)-pyrrolidine trifluoromethanesulfonamide (**1**) is an effective organocatalyst for promoting direct, highly enantio- and/or diastereoselective Michael addition of unmodified aldehydes and ketones to β -nitrostyrenes. The process proceeds under mild reaction conditions to produce versatile γ -nitro aldehydes and ketones. In this investigation, we showed that the Michael addition reactions have broad applicability with respect to both the Michael donors and the acceptors; both aldehydes and ketones and a wide range of nitroolefins can be tolerated. Furthermore, using the **1**-promoted Michael addition as a key step, we have developed an efficient synthesis of Sch50971. A practical three-step preparation of organocatalyst **1** has also been developed and, as a result, its ready availability renders it as a valuable catalyst for asymmetric synthesis.

Computational studies have been conducted to gain an understanding of the origin of the stereoselectivity of **1**-catalyzed the Michael addition process. The results agree quite well with the observed stereoselectivity of **1**-catalyzed Michael addition reactions of aldehydes and ketones and attribute the activity of the organocatalyst to the formation of both intramolecular and intermolecular hydrogen bonds. The preference of the *si* approach for aldehydes appears to stem from the alignment of the bulky sulfonamide group with the β -nitrostyrene, which is in turn determined by the chirality of the C α atom in the catalyst. On the other hand, the preference of the *re* reaction path in ketone reactions seems to originate from the stereo hindrance between the bulky sulfonamide group in the catalyst and an alkyl group in the enamine intermediate. These results provide valuable insight into the mechanisms of asymmetric organocatalysis and might help the design of new and more efficient organocatalysts.

Experimental Section

General: Unless specified, all reactions were performed under an aerobic atmosphere. Commercial, HPLC grade solvents were used directly for reactions without further purification. HPLC grade EtOAc and hexanes were used for column chromatography. Anhydrous THF was obtained from distillation of Na and benzophenone. Column chromatography was performed with silica gel (230–400 mesh size). TLC plates with F₂₅₄ indicator were used for monitoring reactions. The combined organic layers

were dried over MgSO_4 . Solvents were evaporated under reduced pressure. All yields given refer to as isolated yields. ^1H NMR was recorded on a 500 MHz and ^{13}C on a 125 MHz spectrometer. HRMS experiment was performed on a high resolution magnetic sector spectrometer. Tetramethylsilane (TMS) was used as a reference for ^1H NMR experiments. Data for ^1H are reported as follows: chemical shift (ppm), and multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet). Data for ^{13}C NMR are reported as ppm.

Typical procedure for Michael addition reaction of aldehydes: Catalyst **1** (10 mg, 0.044 mmol) was added to a vial containing isobutyraldehyde (0.20 mL, 2.19 mmol) and dry *i*PrOH (1 mL) at 0°C . The mixture was vigorously stirred for 15 min, and then *trans*- β -nitrostyrene (33 mg, 0.219 mmol) was added. After 4.5 d stirring, TLC analysis indicated completion of the reaction. After the reaction mixture was concentrated under reduced pressure, the resulting residue was then purified by silica-gel chromatography (ethyl acetate/hexane=1:30 to 1:5) and fractions were collected and concentrated in vacuo to provide a clear oil (41 mg, 0.186 mmol, 85%). Relative and absolute configurations of the product were determined by comparison with the known ^1H NMR, ^{13}C NMR and optical rotation data (see Supporting Information).

Typical procedure for Michael addition reaction of ketones (Tables 3 and 4): Catalyst pyrrolidine sulfonamide **1** (10 mg, 0.044 mmol) was added to a vial containing cyclohexanone (0.23 mL, 2.19 mmol) and dry *i*PrOH (1.0 mL) at 0°C . The mixture was vigorously stirred for 15 min, and then *trans*- β -nitrostyrene (33 mg, 0.219 mmol) was added. After 10 h stirring, TLC analysis indicated completion of the reaction. After reaction mixture was concentrated under reduced pressure, the resulting residue was then purified by silica-gel chromatography (ethyl acetate/hexane=1:30 to 1:5) and fractions were collected and concentrated in vacuo to provide a white solid (52 mg, 0.210 mmol, 96%). Relative and absolute configurations of the product were determined by comparison with the known ^1H NMR, ^{13}C NMR and optical rotation data (see Supporting Information).

1-(1,1-Diphenylethyl)-1H-imidazole-4-carbaldehyde (11): Chlorotriphenylmethane (1.73 g, 6.3 mmol) was added to a solution of compound **10** (0.5 g, 5.2 mmol) and triethylamine (0.87 mL, 6.3 mmol) in dichloromethane (15 mL) at room temperature; the reaction mixture was stirred for 14 h. After reaction mixture was concentrated under reduced pressure, the resulting residue was then purified by silica-gel chromatography (ethyl acetate/hexane=1:10 to 1:2) and fractions were collected and concentrated in vacuo to provide a white solid (1.67 g, 95%).

4-[(E)-2-Nitrovinyl]-1-(1,1-diphenylethyl)-1H-imidazole (12):^[12] Piperidine (1 drop) and acetic acid (1 drop) were added to a solution of compound **11** (0.2 g, 0.59 mmol) in nitromethane (3 mL) at room temperature; the reaction mixture was stirred for 8 h. After reaction mixture was concentrated under reduced pressure, the resulting residue was then purified by silica-gel chromatography (ethyl acetate/hexane=1:10 to 1:3) and fractions were collected and concentrated in vacuo to afford a pale solid (178 mg, 79%).

(2R,3R)-2-Methyl-4-nitro-3-(1-trityl-1H-imidazol-4-yl)butanal (13): Catalyst **1** (4 mg, 0.02 mmol) was added to a solution of compound **12** (38 mg, 0.1 mmol) and propionaldehyde (73 μL , 1.0 mmol) in dichloromethane (0.5 mL) and *i*PrOH (0.5 mL) at 0°C ; the reaction mixture was stirred for 24 h. After reaction mixture was concentrated under reduced pressure, the resulting residue was then purified by silica-gel chromatography (ethyl acetate/hexane=1:10 to 1:3) and fractions were collected and concentrated in vacuo to afford a white solid (34 mg, 78%). $[\alpha]_{\text{D}}^{25}$ (major)=+44.4 ($c=0.8$ in CHCl_3); ^1H NMR (500 MHz, CDCl_3 , 25°C , TMS): δ =9.72 (s, 1H; CHO), 7.39 (s, 1H; Ar), 7.36–7.30 (m, 9H; Ar), 7.11–7.06 (m, 6H; Ar), 6.63 (s, 1H; Ar), 4.80 (dd, $^3J(\text{H,H})=12.0$ Hz, 8.5 Hz, 1H; CH), 4.72 (dd, $^3J(\text{H,H})=12.0$ Hz, 5.5 Hz, 1H; CH), 3.88 (dd, $^3J(\text{H,H})=15.0$ Hz, 7.5 Hz, 1H; CH), 2.87–2.78 (m, 1H; CH), 1.05 ppm (d, $^3J(\text{H,H})=7.0$ Hz, 3H; CH_3); ^{13}C NMR (125 MHz, 25°C , CDCl_3): δ =202.5, 142.1, 139.1, 136.5, 129.6, 128.1, 128.0, 75.4, 47.4, 37.5, 11.1 ppm; HRMS (EI) calcd for $[\text{C}_{28}\text{H}_{21}\text{N}_3\text{O}_3+\text{Na}]^+$: 219.0620; found: 219.0626; HPLC (Chiralpak AD, *i*PrOH/Hexane=10:90, flow rate 1.0 mL min⁻¹, λ =254 nm): $t_{\text{minor}}=28.3$ min, $t_{\text{major}}=22.1$ min, $ee=99\%$, d.r.=12:1 (after further silica-gel column purification, d.r. was improved to 20:1).

4-[(3R,4R)-4-Methylpyrrolidin-3-yl]-1-trityl-1H-imidazole (14): $\text{Pd}(\text{OH})_2$ (20%; 21 mg, 30%) was added to a solution of compound **13** (70 mg, 0.16 mmol) in methanol (10 mL) and the reaction mixture was reductively cyclized at 45 psi for 96 h. After reaction mixture was concentrated under reduced pressure, the resulting residue was then purified by silica-gel chromatography (methanol/dichloromethane=1:5) and fractions were collected and concentrated in vacuo to afford a clear solid (41 mg, 65%).

4-[(3R,4R)-4-Methylpyrrolidin-3-yl]-1H-imidazole (9; Sch 50971): CF_3COOH (95%, 5 mL) was added to compound **14** (70 mg, 0.18 mmol) and the reaction mixture was stirred for 96 h. After reaction mixture was concentrated under reduced pressure, HCl (1 N, 4 mL) was added to the reaction mixture and products were extracted with Et_2O (3×10 mL). The aqueous phase was concentrated under reduced pressure to afford a white solid (22 mg, 91%). $[\alpha]_{\text{D}}^{25}$ (major)=+36.1 ($c=0.6$ in MeOH), literature value^[21] $[\alpha]_{\text{D}}^{25}$ (major)=+43.5 ($c=0.34$ in MeOH).

Computational methods: All the calculations, including Hartree–Fock (HF) and density functional theory (DFT), were carried out using the Gaussian 03 suite of programs.^[27] The stationary points corresponding to the enamine–nitrostyrene (reactant) complex and the transition state for the C–C bond were fully optimized by using both the HF and DFT approaches. These stationary points were confirmed by additional frequency calculations and the transition state was verified by the existence of an imaginary frequency. The energies reported in this work include the zero-point energy corrections. To confirm the connectivity between the reactant and transition state, intrinsic reaction coordinate (IRC)^[28] calculations were performed. In the DFT calculations, the B3LYP exchange–correlation functional^[29,30] was used and its accuracy in studying asymmetric organocatalysis has been well documented.^[12c] Two basis sets, namely the standard 6–31G* and 6–31G** basis sets, were tested in the DFT calculations and the results are very close (see Supporting Information). As a result, only the 6–31G* results are reported here. Atomic charges were calculated using the CHelpG method.^[31] The solvent effects for the solution phase reaction were estimated for the stationary points using the polarized continuum model (PCM),^[32] with no further geometry optimization. In all of the PCM calculations, the UAKS radii and a dielectric constant of 20 were used to simulate the isopropyl alcohol solvent.

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- [1] (S)-Pyrrolidine trifluoromethanesulfonamide (**1**) has been used for catalyzing: a) Mannich reactions: W. Wang, J. Wang, H. Li, *Tetrahedron Lett.* **2004**, 45, 7243–7246; b) α -aminooxylation: W. Wang, J. Wang, H. Li, L.-X. Liao, *Tetrahedron Lett.* **2004**, 45, 7235–7238; H. Sundén, N. Dahlin, I. Ibrahim, H. Adolfsson, A. Córdova, *Tetrahedron Lett.* **2005**, 46, 3385–; c) aldol: W. Wang, H. Li, J. Wang, *Tetrahedron Lett.* **2005**, 46, 5077–5079; d) Michael addition of ketones to enones: J. Wang, H. Li, L.-S. Zu, W. Wang, *Adv. Synth. Catal.* **2006**, 348, 413–417; e) Michael addition of aldehydes to nitroolefins: W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, 117, 1393–1395; *Angew. Chem. Int. Ed.* **2005**, 44, 1369–1371; f) α -selenenylation: J. Wang, H. Li, Y.-J. Mei, B. Lou, D.-G. Xu, D.-Q. Xie, H. Guo, W. Wang, *J. Org. Chem.* **2005**, 70, 5678–5687; g) α -sulfenylation: W. Wang, H. Li, J. Wang, L.-X. Liao, *Tetrahedron Lett.* **2004**, 45, 8229–8231.

- [2] a) F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463; b) F. G. Bordwell, D. Algrim, *J. Org. Chem.* **1976**, *41*, 2507–2508.
- [3] P. Perlmutter *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, **1992**.
- [4] For recent reviews of asymmetric Michael addition reactions, see: a) N. Krause, A. Hoffmann-Roder, *Synthesis* **2001**, 171–196; b) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894; c) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033–8061; d) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726–1728; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688–1690.
- [5] For selected examples, see: a) T. A. Johnson, D. O. Jang, B. W. Slafer, M. D. Curtis, P. Beak, *J. Am. Chem. Soc.* **2002**, *124*, 11689–11698; b) A. Alexakis, C. Benhaim, *Org. Lett.* **2000**, *2*, 2579–2581; c) T. Hayashi, *Synlett* **2001**, 879–; d) T. Hayashi, T. Senda, M. Ogawara, *J. Am. Chem. Soc.* **2000**, *122*, 10716–10717; e) A. Duursma, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2003**, *125*, 3700–3701; f) A. Duursma, A. J. Minnaard, B. L. Feringa, *Tetrahedron* **2002**, *58*, 5773–5778; g) A. Alexakis, C. Benhaim, S. Rosset, M. Humam, *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263; h) A. Rimkus, N. Sewald, *Org. Lett.* **2003**, *5*, 79–80; i) C. A. Luchaco-Cullis, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 8192–8193; j) D. M. Mampreian, A. H. Hoveyda, *Org. Lett.* **2004**, *6*, 2829–2832; k) H. Choi, Z. Hua, I. Ojima, *Org. Lett.* **2004**, *6*, 2689–2691; l) M. Watanabe, A. Ikagawa, H. Wang, K. Murata, T. Ikariya, *J. Am. Chem. Soc.* **2004**, *126*, 11148–11149; m) D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, J. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13097–13105; n) J. Ji, D. M. Barnes, J. Zhang, S. A. King, S. J. Wittenberger, H. E. Morton, *J. Am. Chem. Soc.* **1999**, *121*, 10215–10216; o) H. Brunner, B. Kimel, *Monatsh. Chem.* **1996**, *127*, 1063–1072.
- [6] A book for discussing organocatalysis, see: A. Berkessel, H. Groger *Asymmetric Organocatalysis-From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, Germany, **2005**.
- [7] For recent reviews of organocatalysis, see: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840–3864; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748; b) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; c) special issue on organocatalysis: *Acc. Chem. Res.* **2004**, *37*, 487–631; d) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724; e) S.-K. Tian, Y.-G. Chen, J.-F. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621–631.
- [8] Cinchona alkaloids as organocatalysts for Michael addition of nitroolefins, see: a) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107–110; *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108; b) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907; c) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525–6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370.
- [9] Amine thioureas as organocatalysts for Michael addition of nitroolefins, see: a) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125; b) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; c) J. Wang, H. Li, W.-H. Duan, L.-S. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713–4716.
- [10] Proline as an organocatalyst for Michael addition of nitroolefins: a) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2425; b) D. Enders, A. Seki, *Synlett* **2002**, 26–28; c) P. Kotrusz, S. Toma, H.-G. Schmalz, A. Alder, *Eur. J. Org. Chem.* **2004**, 1577–1583.
- [11] Pyrrolidine diamines as organocatalysts for Michael addition of nitroolefins, see: a) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527–2530; b) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737–3740; c) J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 4441–4444; d) J. M. Betancort, K. Sakthivel, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Synthesis* **2004**, 1509–1521; e) O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2003**, *5*, 2559–2561; f) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611–3614; g) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147–1168.
- [12] Pyrrolidine tetrazole as organocatalyst for Michael addition of nitroolefins, see: a) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808–1809; b) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84–96; c) A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, 558–560.
- [13] T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559.
- [14] a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215; b) Y. Xu, A. Córdova, *Chem. Commun.* **2006**, 460–462.
- [15] R. M. Burch, R. J. Patch, B. G. Shearer, J. J. Perumattam, K. J. Natalie, Jr (Nova Pharmaceutical Corp., USA) WO 9203415, **1992**.
- [16] L-N-Cbz-proline amide **2** is commercially available from GL Biochem (Shanghai) Ltd., Shanghai China (93 \$ per 25 g).
- [17] a) H. C. Brown, P. Heim, *J. Am. Chem. Soc.* **1964**, *86*, 3566–3567; b) W. V. Curran, R. B. Angier, *J. Org. Chem.* **1966**, *31*, 3867–3868.
- [18] In comparison, for the same reaction, at 4°C (*S*)-pyrrolidine diamine as catalyst gave the product with 80% *ee* (ref. [11a]), while (*S*)-diphenylpyrrolinol TMS ether produced product with 68% *ee* at room temperature (ref. [14]).
- [19] CCDC-287830 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [20] L-Proline: 7% *ee*, reported in reference [10a]; diamine: 29% *ee*, reported in reference [11f]; pyrrolidine tetrazole: 33% *ee*, reported in reference [12a]. Recently, 87% *ee* has been achieved: S. B. Tsogoeva, D. A. Yalalov, M. J. Hateley, C. Weckbecker, K. Huthmacher, *Eur. J. Org. Chem.* **2005**, 4995–5000.
- [21] R. Aslanian, G. Lee, R. V. Iyer, N.-Y. Shih, J. J. Piwinski, R. W. Draper, A. T. McPhail, *Tetrahedron: Asymmetry* **2000**, *11*, 3867–3871.
- [22] a) R. L. McLeod, R. Aslanian, M. Del Prado, R. Duffy, R. W. Egan, W. Kreutner, R. McQuade, J. A. Hey, *J. Pharmacol. Exp. Ther.* **1998**, *287*, 43–50; b) N.-Y. Shih, R. Aslanian, A. T. Lupo, Jr., S. Orlando, J. J. Piwinski, M. J. Green, A. K. Ganguly, R. West, S. Tozzi, W. Kreutner, J. A. Hey, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 243–248; c) I. J. P. De Esch, H. Timmerman, W. M. P. B. Menge, P. H. J. , N. derkoorn, *Arch. Pharm.* **2000**, *333*, 254–260.
- [23] a) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283; b) M. Arno, L. R. Domingo, *Theor. Chem. Acc.* **2002**, *108*, 232–239; c) K. N. Rankin, J. W. Gauld, R. J. Boyd, *J. Phys. Chem. A* **2002**, *106*, 5155–5159; d) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479; e) Z. Tang, F. Jiang, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5755–5760; f) F. R. Clemente, K. N. Houk, *Angew. Chem.* **2004**, *116*, 5890–5892; *Angew. Chem. Int. Ed.* **2004**, *43*, 5766–5768; g) F. R. Clemente, K. N. Houk, *J. Am. Chem. Soc.* **2005**, *127*, 11294–11302; h) C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558–569.
- [24] B. List, R. A. Lerner, C. F. , Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
- [25] J. L. Reymond, *J. Mol. Catal. B* **1998**, *5*, 331–337.
- [26] R. B. Silverman *The Organic Chemistry of Enzyme-Catalyzed Reactions*, Academic Press, San Diego, **2002**.
- [27] Gaussian 03, Revision A.1; M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. V. K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakr-

- zewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc.: Pittsburgh, PA, **2003**.
- [28] C. Gonzalez, H. B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523–5527.
- [29] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.
- [30] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.
- [31] C. M. Breneman, K. B. Wiberg, *J. Comput. Chem.* **1990**, *11*, 361–373.
- [32] J. Tomasi, M. Persico, *Chem. Rev.* **1994**, *94*, 2027–2094.

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