Asymmetric Organocatalysis

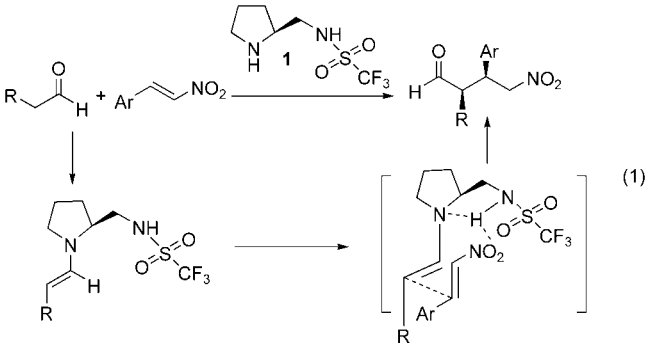
Direct, Highly Enantioselective Pyrrolidine Sulfonamide Catalyzed Michael Addition of Aldehydes to Nitrostyrenes**

Wei Wang, Jian Wang, and Hao Li*

Dedicated to Professor Victor J. Hruby on the occasion of his 65th birthday

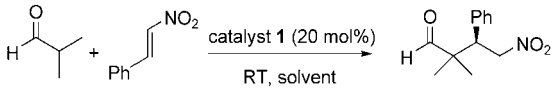
The Michael addition reaction is without question one of the most general and versatile methods for formation of C–C bonds in organic synthesis.[1] Thus, it is not surprising that the development of enantioselective catalytic protocols for this cornerstone reaction has received much attention.[2] Efforts aimed at achieving asymmetric versions of the process by using chiral organocatalysts have been explored intensively in recent years.[3] L-Proline and other pyrrolidine-based catalytic systems for asymmetric Michael reactions have been described, but only moderate enantioselectivities are typically observed.[4,5] As a result, the design and development of new and efficient chiral organocatalysts to achieve high levels of enantio- and/or diastereoselectivity in Michael conjugate additions remain a major challenge in synthetic organic chemistry.[6–9] Recently, Kotsuki and his co-workers described a chiral pyrrolidine–pyridine catalyst that promoted highly enantio- and diastereoselective Michael addition reactions of ketones with nitrostyrenes.[10] However, poor enantioselectivity (ca. 22% *ee*) resulted when an aldehyde was used as the substrate. Herein, we describe the chiral pyrrolidine sulfonamide **1**, which catalyzes the Michael conjugate additions of aldehydes to nitrostyrenes with high levels of enantio- (89–99% *ee*) and diastereoselectivity (≥20:1 d.r.).

As part of a program aimed at developing new organocatalysts for asymmetric organic transformations, we recently observed that the pyrrolidine sulfonamide **1** serves as an efficient catalyst for α-aminoxylation and Mannich-type reactions.[11,12] These processes take place with exceptionally high levels of enantio- and/or diastereoselectivity. Moreover, the catalyst also shows high activity for α-sulfenylation reactions of aldehydes and ketones.[13] Based on these observations, we envisioned that the (*S*)-pyrrolidine sulfonamide **1** would react with an aldehyde to form a chiral enamine, which could serve as a Michael donor in reactions with nitroolefins. In addition, a model inspection suggested that the process would take place by the preferential enamine addition to the less hindered *Si* face of the nitroolefin [Eq. (1)]. Consequently, high levels of enantio- and/or diastereoselectivity are expected. In addition, the bifunctional nature of catalyst **1**, which possesses an acidic sulfonamide[14] and a basic pyrrolidine group, could be expected to lead to high catalytic activities even in the absence of an acidic additive. Herein, we describe the results of the studies using **1** to promote highly enantio- and diastereoselective Michael addition reactions.



The reaction of isobutyraldehyde with *trans*-β-nitrostyrene in the presence of the pyrrolidine sulfonamide **1** (20 mol%) in various solvents at room temperature was investigated initially. As evident in Table 1, the reaction yields varied significantly in the solvents tested. In general, the reaction proceeded more rapidly in polar solvents. For example, in dimethyl sulfoxide (DMSO), isopropyl alcohol (*i*PrOH), *N*,*N*-dimethylformamide (DMF), and MeCN (Table 1, entries 1–5), high yields (64–93%) were obtained, whereas reactions in less polar THF and 1,4-dioxane were very sluggish (Table 1, entries 7 and 8). Interestingly, regardless of the solvents used, the reactions were highly enantioselective (63–83% *ee*). The use of *i*PrOH led to the highest *ee* value (83%), which was further increased to 90% *ee* when the reaction temperature was lowered to 0°C without a significant reduction in the reaction rate (Table 1, entry 3).

Table 1: Effect of solvents on the asymmetric Michael addition reaction of isobutyraldehyde to *trans*-β-nitrostyrene.[a]



Entry	Solv.	*t* [d]	Yield [%][b]	*ee* [%][c]
1	DMSO	2	93	63
2	*i*PrOH	3	89	83
3	*i*PrOH[d]	4.5	85	90
4	DMF	3	87	73
5	CH_3CN	3	64	73
6	CH_3NO_2	3	37	71
7	THF	3	<10	n.d.[e]
8	1,4-dioxane	3	<10	n.d.[e]
9	$CHCl_3$	3	43	79

[a] For reaction conditions see the Experimental Section. [b] Yield of isolated product. [c] Determined by chiral high-performance liquid chromatography (HPLC) analysis (Chiralpak AS-H). [d] Reaction conducted at 0°C. [e] Not determined.

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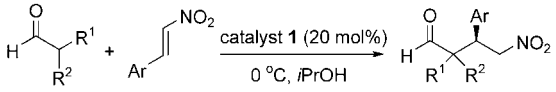
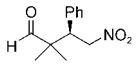
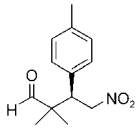
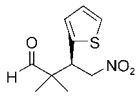
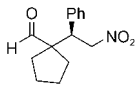
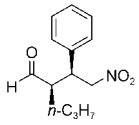
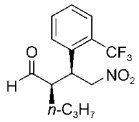
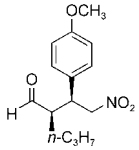
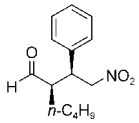
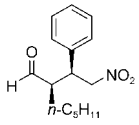
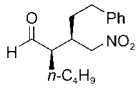
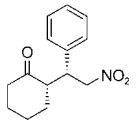
Encouraged by these results, we next probed the scope of the reaction with a variety of aldehydes and nitroolefins (Table 2). All reactions were conducted in *i*PrOH at 0 °C in the presence of 20 mol % of **1**. In each case, smooth reactions occurred to generate Michael adducts in high yields (63–99 %), high enantioselectivities (89–99 % *ee*), and excellent diastereoselectivities (d.r. ≥ 20:1). Variations in the nitrostyrenes used in reaction with isobutyraldehyde had no effect on the enantioselectivities (Table 2, entries 1–3). Reaction of the more bulky cyclopentanecarboxaldehyde gave even higher enantioselectivity (93 % *ee*) and yield (89 %) (Table 2, entry 4). More significantly, catalyst **1** catalyzed reactions of linear chain aldehydes yielded adducts with excellent enantioselectivity (94–99 % *ee*), diastereoselectivity (≥ 20:1 d.r.), and high yields (63–99 %, Table 2, entries 5–9). In these processes, two adjacent stereogenic centers were generated with complete stereocontrol. Again, changes in the electronic properties of the nitroolefins (Table 2, entries 5–7) and steric demands of the aldehydes (Table 2, entries 5, 8, and 9) had only a small effect on the stereoselectivities and yields. The aliphatic nitroolefin *trans*-Ph$(CH_2)_2$CH=$CHNO_2$ provided the desired product in good yield (76 %) and high diastereoselectivity (50:1 d.r.), but poor enantioselectivity (22 % *ee*, Table 2, entry 10). The relative and absolute configurations of the Michael adducts were determined by comparison with ^{1}H NMR spectroscopic analysis and optical rotation studies of known compounds.[15]

Table 2: Michael addition reactions of aldehydes to *trans*-β-nitrostyrenes catalyzed by **1**.



Entry	Product	*t* [h]	Yield [%][a]	*ee* [%][b]	d.r.[c]
1		4.5	85	90	–
2		6	67	90	–
3		6	75	89	–
4		42	89	93	–
5		20	99	96	50:1
6		28	63	94	22:1
7		24	86	99	20:1
8		24	94	99	30:1
9		26	91	97	50:1
10		24	76	22	50:1
11		10	96	97	50:1

[a] Yield of isolated product. [b] Determined by chiral high-performance liquid chromatography analysis (Chiralpak AS-H, or AD and Chiralcel OD-H). [c] Determined by ^{1}H NMR spectroscopic analysis.

The results of a preliminary study demonstrated that **1** also catalyzed Michael addition reactions of ketones (Table 2, entry 11). Under the reaction conditions described above, the addition of cyclohexanone to *trans*-β-nitrostyrene resulted in the formation of the adduct in 96 % yield, 97 % *ee*, and 50:1 d.r.

In conclusion, we have found that the pyrrolidine sulfonamide organocatalyst **1** can be used to promote highly efficient, asymmetric Michael addition reactions of aldehydes and ketones to nitroolefins. In these transformations, **1** exhibits a high catalytic activity that takes place with excellent diastereo- and enantioselectivity. The full scope of this new catalytic reaction is currently being investigated.

Experimental Section

Typical procedure: The catalyst pyrrolidine sulfonamide **1** (10 mg, 0.044 mmol) was added to a vial containing *n*-hexanal (0.27 mL, 2.19 mmol) and *i*PrOH (1.0 mL) at 0 °C. The mixture was stirred vigorously for 15 min, and then *trans*-β-nitrostyrene (33 mg, 0.22 mmol) was added. After 24 h of stirring, the reaction mixture was concentrated in vacuo. The residue was purified by flash silica gel chromatography (ethyl acetate/hexane = 1:30) to afford 51 mg (94 %) of the adduct as a clear oil; 30:1 d.r. (by ^{1}H NMR) and 99 % *ee*, (chiral HPLC, Chiralcel OD-H column, $\lambda = 254$ nm, 20 % *i*PrOH/hexane at 1.0 mL min^{-1}, $t_R = 10.4$ min (minor) and 11.8 min (major)); $[\alpha]_D$(major) = +52.4 ($c = 0.5$ in $CHCl_3$), ref. [5a] $[\alpha]_D = +33.4$ ($c = 1.4$ in $CHCl_3$).

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[15] For further details, see the Supporting Information.

