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A Novel Bifunctional Sulfonamide Primary Amine-Catalyzed Enantioselective Conjugate Addition of Ketones to Nitroolefins

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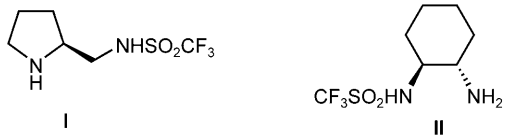
Abstract: The enantioselective conjugate addition of a variety of ketones to nitroolefins has been developed. The process is efficiently catalyzed by a novel bifunctional sulfonamide primary amine in good yields and with good levels of enantioselectivity.

Keywords: conjugate addition; ketones; nitroolefins; organocatalysis; sulfonamide primary amine

Organocatalytic asymmetric reactions have proved to be efficient and powerful tools in organic synthesis.[1] Among them, Michael addition reactions, one of the most important and versatile processes for the synthesis of new C–C and C–X bonds, have been intensively studied with organocatalysis.[2] The catalysts typically used for these processes are proline and its analogue-derived secondary amines.[3] It is noted that, generally, good enantio- and diastereoselectivity is obtained only for aldehydes and cyclohexanone as nucleophiles. However, poor catalytic activity and stereoselectivity are observed for acyclic ketones.[3] It is more problematic for aromatic ketones, and generally no reactions occur. Therefore, the development of new organocatalysts which are able to catalyze these difficult substrates is an important, but formidable and challenging task in order to significantly expand the scope of organocatalyzed conjugate addition reactions.

Recently, primary amine catalysts have emerged to be effective promoters for organic processes including Michael addition,[4] aldol,[5] α-aminations[6] and cycloaddition reactions.[7] The notable feature of primary amine catalysts is that they can activate aromatic ketones[4c,e] and α,α-disubstituted aldehydes.[4d] Jacobsen and co-workers have developed an elegant highly enantioselective conjugate addition of acyclic ketones[4c] and α,α-disubstituted aldehydes[4d] to nitroalkenes by applying a chiral primary amine-thiourea catalyst. Herein we wish to report a new simple bifunctional sulfonamide primary amine organocatalyst that promotes Michael addition reactions while achieving a respected level of enantioselectivity. Significantly, the processes are applicable to a variety of ketones as Michael donors.

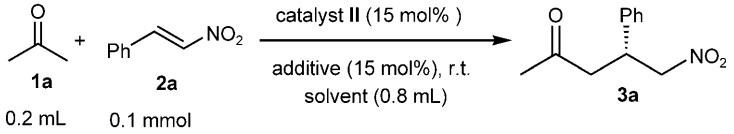
We have developed (*S*)-pyrrolidine trifluoromethanesulfonamide **I** as a general organocatalyst for promoting a variety of asymmetric organic transformations with high efficiency (Figure 1).[8] As demonstrated, in many cases, the catalyst is superior to proline in terms of catalytic activity and stereoselectivity toward organic processes. It is believed that its high catalytic efficiency is attributable to its unique activation mode,[8d,g] arising from the trifluoromethanesulfonamide moiety. This functionality affords two H-bond forces for activation of substrates and formation of a well-controlled transition state. Inspired by the proven ability of the sulfonamide group in highly effective asymmetric conjugate addition reactions,[8d,g,i]



I II

Figure 1. Bifunctional sulfonamide amine organocatalysts.

Table 1. Optimization of reaction conditions.



Entry	Solvent	Additive	Time [h]	Yield[a] [%]	*ee*[b] [%]
1	DMF	TEA	30	63	−13
2	DMSO	TEA	18	34	−24
3	CH_3CN	TEA	156	53	25
4	acetone	TEA	144	72	17
5	THF	TEA	240	53	10
6	*i*PrOH	TEA	84	68	−7
7	EtOAc	TEA	240	63	46
8	H_2O	TEA	72	0	nd[c]
9	CH_2Cl_2	TEA	156	93	65
10	$CHCl_3$	TEA	72	92	71
11	$CHCl_3$	AcOH	72	84	72
12	$CHCl_3$	H_2O	72	92	72
13	$CHCl_3$	none	54	87	65
14[d]	$CHCl_3$	none	54	58	87
15[e]	$CHCl_3$	H_2O	72	93	70

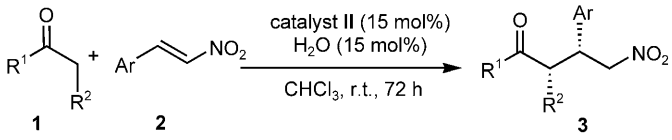
[a] Isolated yield.
[b] Determined by chiral HPLC analysis (Chiralpak AS-H).
[c] Not determined.
[d] Reaction was performed at 0 °C.
[e] Reaction was performed at 0.5 M of **2a**.

we envisioned that the incorporation of the moiety into a chiral *trans*-cyclohexane diamine scaffold would result in a new bifunctional sulfonamide primary amine organocatalyst **II**.[9] The catalyst could be useful for effecting the Michael addition of ketones to nitroolefins.

To probe the feasibility of **II**-catalyzed direct conjugate addition of ketones to nitroolefins, a model reaction between acetone and *trans*-β-nitrostyrene was explored (Table 1). Initially, the reaction was carried out by using 15 mol% of catalyst **II** with triethylamine (TEA) as an additive in various solvents. In polar aprotic solvents, such as DMF and DMSO (Table 1, entries 1 and 2), the process was completed in a relatively short time but with low or moderate yield and poor enantioselectivity. It was also found that other solvents, such as CH_3CN, acetone, THF, *i*-PrOH and EtOAc, were not suitable for the process (entries 3–7); in these cases a long reaction time was required to obtain acceptable yields, alebit with unsatisfied *ee*s (7–46%). Water as reaction medium was probed for the reaction, and no reaction took place (entry 8). To our delight, the conjugate addition reaction proceeded well in high yields (> 90%) and moderate enantioselectivity (65% and 71% *ee* respectively, entries 9 and 10) with CH_2Cl_2 and $CHCl_3$ as solvent.

Further optimization of reaction conditions using $CHCl_3$ as solvent was carried out next. A survey of additives revealed that they played a certain role in governing reaction yields and enantioselectivity (entries 10–13). Interestingly, no matter what additives were used, better outcomes (entries 10–12) were obtained than those without an additive (entry 13). Water as an additive was beneficial to the process in terms of reaction yield and enantioselectivity (entry 12). It is believed that water can increase the catalyst turnover presumably due to facilitating the release of the primary catalyst from the imine.[10] On the other hand, based on our early studies,[8d,g] it was found that water could enhance the enantioselectivity of chiral trifluoromethanesulfonamide amine-catalyzed reactions because the trifluoromethanesulfonamide moiety provides two H-bond interactions for activation of substrates and formation of a well-controlled transition state. One of H-bond networks involves water, the "O" of SO_2 and the carbonyl group of the substrate.[8d,g] Lowering the reaction temperature led to an improvement of the enantioselectivity but with a significant loss of yield (entry 14). These studies prompted us to select water as an additive and room temperature as optimized reaction conditions to probe the scope of the conjugate addition processes. The absolute stereoconfiguration of the product **3a** was determiend based on the comparision of the optical rotation of its known counterpart.[11]

Table 2. Scope of **II**-catalyzed conjugate addition of ketones to nitrostyrenes.[a]



1 2 3

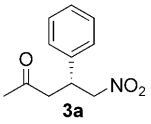
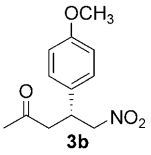
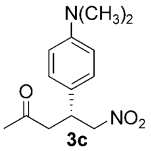
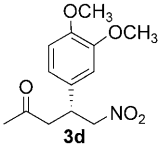
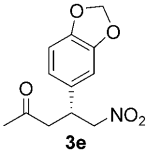
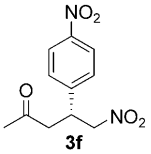
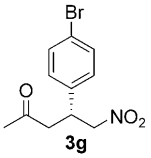
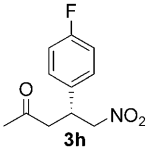
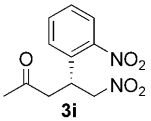
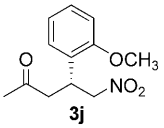
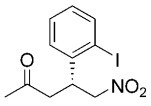
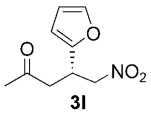
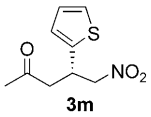
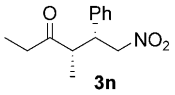
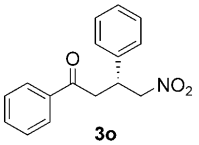
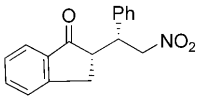
Entry	Product	Yield[b] [%]	*ee*[c] [%]
1	 **3a**	92	72
2	 **3b**	84 (25)[d]	80 (93)[d]
3	 **3c**	64	87
4	 **3d**	94	85
5	 **3e**	65	84
6	 **3f**	80	57
7	 **3g**	87	68
8	 **3h**	93	69
9	 **3i**	67	57
10	 **3j**	89	69

Table 2. (Continued)

Entry	Product	Yield[b] [%]	*ee*[c] [%]
11	 **3k**	88	71
12	 **3l**	86	78
13	 **3m**	94	75
14[e]	 **3n**	33[f]	96 (*syn*); 85 (*anti*)
15[g]	 **3o**	46	82
16[h]	 **3p**	33[i]	87 (*syn*)

[a] Unless specified, see experimental section for reaction conditions.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralcel AS-H, AD-H and OD-H).
[d] Reaction was carried out in an ice bath.
[e] *Conditions:* 3-pentanone (0.6 mL), nitroolefin (0.30 mmol), cat. (30 mol%), $CHCl_3$ (1.2 mL) and water (15 mol%), at room temperature for 72 h.
[f] *syn:anti* = 1:1, determined by ^1H NMR analysis.
[g] *Conditions:* acetophenone (0.2 mL), nitroolefin (0.20 mmol), cat. (15 mol%), $CHCl_3$ (0.4 mL), at room temperature for 72 h.
[h] *Conditions:* 1-indanone (0.2 mmol), nitroolefin (0.10 mmol), cat. (30 mol%), $CHCl_3$ (0.2 mL), at room temperature for 120 h.
[i] *syn : anti* = 3:1, determined by ^1H NMR analysis.

As summarized in Table 2, generally, the **II**-catalyzed Michael addition reactions proceeded smoothly with a wide range of ketones and nitroalkenes. First, the conjugate additions of acetone to a variety of nitroolefins were examined (Table 2, entries 1–13). It was found that electronic nature of the substituents of the nitroolefin had an effect on enantioselectivity. High enantioselectivities (80–87% *ee*, entries 2–5) were achieved with electron-rich substituents, while those bearing electron-deficient substituents gave only moderate enantioselectivities (57–69% *ee*, entries 6–8). On the other hand, steric hindrance had

little effect on the conjugate addition processes. Substituents at the *ortho*-position of the aromatic systems in nitroolefins had a limited impact on enantioselectivity (57–71% *ee*, entries 9–11). Heteroaromatic nitroolefins were also good Michael acceptors and the reactions provided high yields and good enantioselectivities (entries 12 and 13).

Next, some challenging ketones were investigated as Michael donors for the **II**-catalyzed conjugate addition reactions. It is realized that the addition of 3-pentanone to nitrostyrene has puzzled chemists for a long time. Poor enantioselectivities were obtained by using various pyrrolidine-based secondary amines as catalysts. However, the reaction worked very well with primary amine catalysts according to the results reported by Jacobsen[4a] and Connon.[4g] We demonstrated that our catalytic system was also good for the conjugate addition reaction to give high enantioselectivities (96% and 85% *ee* for *syn* and *anti* isomers respectively) in spite of poor diastereoselectivity (1:1 *dr*) and yield (entry 14). The conjugate addition of aromatic ketones to nitrostyrene was another formidable challenge to chemists, and until now, only two catalytic systems were efficient in this reaction.[4a,c] We were glad to find that the catalyst **II** also enabled us to promote the addition of acetophenone to nitrostyrene in moderate yield and high enantioselectivity (entry 15). Encouraged by this result, we further first probed 1-indanone as a substrate, which has not been explored for the Michael addition reaction. To our delight, the process took place efficiently and afforded the desired product with moderate *dr* (3:1) and high *ee* (entry 16).

In conclusion, we have developed a novel bifunctional chiral *trans*-cyclohexanediamine-based sulfonamide primary amine catalyst. The above studies have demonstrated that the catalyst is capable of promoting efficient conjugate additions of acetone to a wide range of nitroolefins. Moreover, this catalytic system can be applied to some challenging ketones such as 3-pentanone, acetophenone and 1-indanone. Further efforts on improvement of the enantio- and diastereoselectivity of the conjugate addition processes by modification of this class of catalysts and the exploration of other valuable organic transformations are under active investigation.

Experimental Section

Typical Procedure (Table 2, entry 1)

A mixture of *trans*-β-nitrostyrene **2a** (0.10 mmol), acetone (0.2 mL), catalyst **II** (15 mol%), $CHCl_3$ (0.8 mL) and water (15 mol%) was stirred at room temperature for 72 h. The reaction mixture was concentrated un vacuum. The residue was purified by flash silica gel chromatography (ethyl acetate/hexane = 1:6) to afford the adduct **3a** as a white solid; yield: 19 mg (92%); 72% *ee*, determined by HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 40/60, flow rate 1.0 mL min^{-1}, $\lambda = 210$ nm, 25 °C): $t_{mino}r = 8.2$ min, $t_{major} = 10.4$ min; $[\alpha]_D^{23}$: +183.3 (*c* 1.0 in $CHCl_3$).

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